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(54) Title: N-ACYLPIPERIDINE TACHYKININ ANTAGONISTS (57) Abstract <p>N-Acylpiperidines of general structure (I) are tachykinin receptor antagonists useful in the treatment of inflammatory diseases, pain or migraine, asthma and emesis.</p> <div data-bbox="1055 1113 1412 1512"><p style="text-align: right;">(I)</p></div>		

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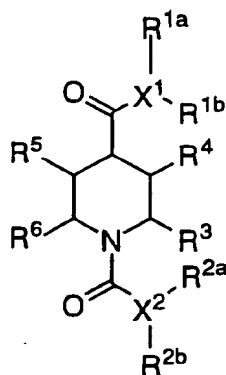
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TITLE OF THE INVENTION

N-ACYLPIPERIDINE TACHYKININ ANTAGONISTS

SUMMARY OF THE INVENTION

This invention is concerned with novel compounds represented by structural Formula I:



I

wherein X¹, X², R^{1a}, R^{1b}, R^{2a}, R^{2b}, R³, R⁴, R⁵, and R⁶ are hereinafter defined.

The invention is also concerned with pharmaceutical formulations with these novel compounds as active ingredients and the use of the novel compounds and their formulations in the treatment of certain disorders.

The compounds of this invention have activity as tachykinin receptor antagonists and are useful in the treatment of inflammatory diseases, pain or migraine, asthma and emesis.

Also, some of these compounds are calcium channel blockers and are useful in the treatment of cardiovascular disorders such as angina, hypertension or ischemia.

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BACKGROUND OF THE INVENTION

Analgesia has historically been achieved in the central nervous system by opiates and analogs which are addictive, and peripherally by cyclooxygenase inhibitors that have gastric side effects. Substance P antagonists may induce analgesia both centrally and peripherally. In addition, substance P antagonists are inhibitory of neurogenic inflammation.

The neuropeptide receptors for substance P (neurokinin-1; NK-1) are widely distributed throughout the mammalian nervous system (especially brain and spinal ganglia), the circulatory system and peripheral tissues (especially the duodenum and jejunum) are involved in regulating a number of diverse biological processes. This includes sensory perception of olfaction, vision, audition and pain, movement control, gastric motility, vasodilation, salivation, and micturition (B. Pernow, *Pharmacol. Rev.*, 1983, 35, 85-141). The NK-1 and NK-2 receptor subtypes are implicated in synaptic transmission (Laneuville *et al.*, *Life Sci.*, 42: 1295-1305 (1988)).

The receptor for substance P is a member of the superfamily of G protein-coupled receptors. This superfamily is an extremely diverse group of receptors in terms of activating ligands and biological functions. In addition to the tachykinin receptors, this receptor superfamily includes the opsins, the adrenergic receptors, the muscarinic receptors, the dopamine receptors, the serotonin receptors, a thyroid-stimulating hormone receptor, a luteinizing hormone-choriogonadotropic hormone receptor, the product of the oncogene ras, the yeast mating factor receptors, a Dictyostelium cAMP receptor, and receptors for other hormones and neurotransmitters (see A. D. Hershey, *et al.*, *J. Biol. Chem.*, 1991, 226, 4366-4373).

Substance P (also called "SP" herein) is a naturally occurring undecapeptide belonging to the tachykinin family of peptides, the latter being so-named because of their prompt contractile action on extravascular smooth muscle tissue. The tachykinins are distinguished by a conserved carboxyl-terminal sequence Phe-X-Gly-Leu-Met-NH₂.

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In addition to SP the known mammalian tachykinins include neurokinin A and neurokinin B. The current nomenclature designates the receptors for SP, neurokinin A, and neurokinin B as NK-1, NK-2, and NK-3, respectively.

More specifically, substance P is a pharmacologically-active neuropeptide that is produced in mammals and possesses a characteristic amino acid sequence (Chang *et al.*, *Nature New Biol.*, 232, 86 (1971); D. F. Veber *et al.*, U.S. Patent No. 4,680,283).

Substance P acts as a vasodilator, a depressant, stimulates salivation and produces increased capillary permeability. It is also capable of producing both analgesia and hyperalgesia in animals, depending on dose and pain responsiveness of the animal (see R.C.A. Frederickson *et al.*, *Science*, 199, 1359 (1978); P. Oehme *et al.*, *Science*, 208, 305 (1980)) and plays a role in sensory transmission and pain perception (T. M. Jessell, *Advan. Biochem. Psychopharmacol.*, 28, 189 (1981)). For example, substance P is believed *inter alia* to be involved in the neurotransmission of pain sensations [Otsuka *et al.*, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in 1982 *Substance P in the Nervous System*, Ciba Foundation Symposium 91, 13-34 (published by Pitman) and Otsuka and Yanagisawa, "Does Substance P Act as a Pain Transmitter?" *TIPS* (Dec. 1987) 8, 506-510]. In particular, substance P has been shown to be involved in the transmission of pain in migraine (see B.E.B. Sandberg *et al.*, *Journal of Medicinal Chemistry*, 25, 1009 (1982)), and in arthritis (Levine *et al.*, *Science*, (1984) 226 547-549). These peptides have also been implicated in gastrointestinal (GI) disorders and diseases of the GI tract, such as inflammatory bowel disease, ulcerative colitis and Crohn's disease, etc. (see Mantyh *et al.*, *Neuroscience*, 25 (3), 817-37 (1988) and D. Regoli in "Trends in Cluster Headache" Ed. F. Sicuteri *et al.*, Elsevier Scientific Publishers, Amsterdam, 1987, pp. 85-95).

Substance P may play a role in a neurogenic mechanism for arthritis (Kidd *et al.*, "A Neurogenic Mechanism for Symmetric Arthritis" in *The Lancet*, 11 November 1989 and Gronblad *et al.*, "Neuropeptides in Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in *J.*

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Rheumatol. (1988) 15(12) 1807-10). Therefore, substance P may be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis (O'Byrne *et al.*, in *Arthritis and Rheumatism* (1990) 33 1023-8).

Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases, proliferative vitreoretinopathy, irritable bowel syndrome and disorders of bladder function including cystitis and bladder detrusor hyperreflexia is reviewed in "Tachykinin Receptors and Tachykinin Receptor Antagonists," C. A. Maggi, R. Patacchini, P. Rovero and A. Giachetti, *J. Auton. Pharmacol.*, (1993) 13, 23-93. Neurokinin-1 receptor antagonists alone or in combination with bradykinin receptor antagonists may also be useful in the prevention and treatment of inflammatory conditions in the lower urinary tract, especially cystitis (Giuliani, *et al.*, *J. Urology*, 150, 1014-1017 (1993)). Other disease areas where tachykinin antagonists are believed to be useful are allergic conditions (Hamelet *et al.*, *Can. J. Pharmacol. Physiol.*, (1988) 66, 1361-7), immunoregulation (Lotz *et al.*, *Science* (1988) 241, 1218-21, Kimball *et al.*, *J. Immunol.* (1988) 141 (10) 3564-9 and A. Perianin, *et al.*, *Biochem. Biophys. Res Commun.* 161, 520 (1989)) vasodilation, bronchospasm, reflex or neuronal control of the viscera (Mantyh *et al.*, *PNAS* (1988) 85 3235-9) and, possibly by arresting or slowing β -amyloid-mediated neurodegenerative changes (Yankner *et al.*, *Science*, (1990) 250, 279-82) in senile dementia of the Alzheimer type, Alzheimer's disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis [J. Lubner-Narod *et al.*, poster presented at C.I.N.P. XVIIIth Congress, 28th June-2nd July, 1992, in press]. Antagonists selective for the neurokinin-1

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(NK-1) and/or the neurokinin-2 (NK-2) receptor may be useful in the treatment of asthmatic disease (Frossard *et al.*, *Life Sci.*, 49, 1941-1953 (1991); Advenier, *et al.*, *Biochem. Biophys. Res. Comm.*, 184(3), 1418-1424 (1992)). Tachykinin antagonists may also be useful in the treatment of small cell carcinomas, in particular small cell lung cancer (SCLC) (Langdon *et al.*, *Cancer Research* (1992) 52, 4554-7).

It has furthermore been suggested that tachykinins have utility in the following disorders: depression, dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and Reynauld's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorder related to immune enhancement or suppression such as systemic lupus erythmatosis (EPO Publication No. 0.436.334) conjunctivitis, vernal conjunctivitis, contact dermatitis, atropic dermatitis, urticaria, and other eczematoid dermatitis (EPO Publication No. 0.394.989) and emesis (*Trends Pharmacol. Sci.*, 9, 334-341 (1988); *Eur. J. Pharmacol.*, 249, R3-R4 (1993)).

Substance P antagonists may be useful in mediating neurogenic mucus secretion in mammalian airways and hence provide treatment and symptomatic relief in diseases characterized by mucus secretion, in particular, cystic fibrosis [S. Ramnarine, *et al.*, abstract presented at 1993 ALA/ATS Int'l Conference, 16-19 May, 1993, published in *Am. Rev. of Respiratory Dis.*, May 1993, in press].

In the recent past, some attempts have been made to provide peptide-like substances that are antagonists for substance P and other tachykinin peptides in order to more effectively treat the various disorders and diseases listed above. See for example Lowe, *Drugs of the Future*, 17 (12) 1115-1121 (1992) and European patent applications (EPO Publication Nos. 0.347.802, 0.401.177 and 0.412.452) which disclose various peptides as neurokinin A antagonists. Also, PCT Patent Publication WO 93/14113 discloses certain peptides as tachykinin antagonists. In addition, EPO Publication No. 0.336.230 discloses

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heptapeptides which are substance P antagonists useful in the treatment of asthma. Merck U.S. Patent No. 4,680,283 also discloses peptidal analogs of substance P.

5 Certain inhibitors of tachykinins have been described in U.S. Patent No. 4,501,733, by replacing residues in substance P sequence by Trp residues.

A further class of tachykinin receptor antagonists, comprising a monomeric or dimeric hexa- or heptapeptide unit in linear or cyclic form, is described in GB-A-2216529.

10 The peptide-like nature of such substances make them too labile from a metabolic point of view to serve as practical therapeutic agents in the treatment of disease. The non-peptidic antagonists of the present invention, on the other hand, do not possess this drawback, as they are expected to be more stable from a metabolic point of view than the previously-discussed agents.

15 It is known in the art that baclofen (β -(aminoethyl)-4-chlorobenzenepropanoic acid) in the central nervous system effectively blocks the excitatory activity of substance P, but because in many areas the excitatory responses to other compounds such as acetylcholine and glutamate are inhibited as well, baclofen is not considered a specific substance P antagonist. Pfizer WIPO patent applications (PCT Publication Nos. WO 90/05525, WO 90/05729, WO 91/18899, WO 92/12151 and WO 92/12152) and publications (*Science*, 251, 435-437 (1991); *Science*, 251, 437-439 (1991); *J. Med. Chem.*, 35, 2591-2600 (1992)) disclose 2-arylmethyl-3-substituted amino-quinuclidine derivatives which are disclosed as being useful as substance P antagonists for treating gastrointestinal disorders, central nervous system disorders, inflammatory diseases and pain or migraine. A Glaxo European patent application (EPO Publication No. 0,360,390) discloses various spiro lactam-substituted amino acids and peptides which are antagonists or agonists of substance P. A Pfizer WIPO patent application (PCT Publication No. WO 92/06079) discloses fused-ring analogs of nitrogen-containing nonaromatic heterocycles as useful for the treatment of diseases mediated by an excess of substance P. A Pfizer WIPO patent

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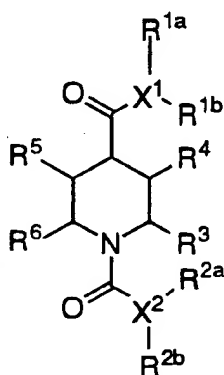
application (PCT Publication No. WO 92/15585) discloses 1-azabicyclo[3.2.2]nonan-3-amine derivatives as substance P antagonists. A Pfizer WIPO patent application (PCT Publication No. WO 93/10073) discloses ethylenediamine derivatives as substance P antagonists. PCT Publication No. WO 93/01169 discloses certain aromatic compounds as tachykinin receptor antagonists. A Sanofi publication (*Life Sci.*, 50, PL101-PL106 (1992)) discloses a 4-phenyl piperidine derivative as an antagonist of the neurokinin A (NK-2) receptor.

Howson *et al.*, (*Biorg. & Med. Chem. Lett.*, 2 (6), 559-564 (1992)) disclose certain 3-amino and 3-oxy quinuclidine compounds and their binding to substance P receptors. EPO Publication 0.499.313 discloses certain 3-oxy and 3-thio azabicyclic compounds as tachykinin antagonists. U.S. Patent No. 3,506,673 discloses certain 3-hydroxy quinuclidine compounds as central nervous system stimulants. A Pfizer EPO Patent application (EPO Publication 0.436.334) discloses certain 3-aminopiperidine compounds as substance P antagonists. U.S. Patent No. 5,064,838 discloses certain 1,4-disubstituted piperidinyll compounds as analgesics. PCT Publication No. WO 92/12128 discloses certain piperidine and pyrrolidine compounds as analgesics. Peyronel, *et al.*, (*Biorg & Med. Chem. Lett.*, 2 (1), 37-40 (1992)) disclose a fused ring pyrrolidine compound as a substance P antagonist. EPO Publication No. 0.360.390 discloses certain spirolactam derivatives as substance P antagonists. EPO Publication No. 0.532.456 discloses certain 1-acyl-piperidine derivatives as substance P antagonists. EPO Publication No. 0.559.538 discloses quaternary salts of certain 4-substituted piperidines as neurokinin antagonists. U.S. Patent No. 4,804,661 discloses certain piperazine compounds as analgesics. U.S. Patent No. 4,943,578 discloses certain piperazine compounds useful in the treatment of pain. PCT Publication No. WO 92/01679 discloses certain 1,4-disubstituted piperazines useful in the treatment of mental disorders in which a dopaminergic deficit is implicated. PCT Publication No. WO 92/21360 and Mills, *et al.*, (*Bioorganic & Med. Chem. Ltr.*, 3 (12) 2707-2712 (1993)) disclose certain 1,4-diacylpiperazine substance P receptor antagonists.

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DETAILED DESCRIPTION OF THE INVENTION

The novel compounds of this invention are represented by structural Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

R^{1a} is selected from the group consisting of:

- 1) H,
- 2) C₁₋₈ alkyl,
- 3) phenyl, either unsubstituted or substituted with one or two substituents selected from the group consisting of:
 - a) -C₁₋₄ alkyl,
 - b) -halo,
 - c) -OH,
 - d) -CF₃,
 - e) -NH₂,
 - f) -NH(C₁₋₄ alkyl),
 - g) -N(C₁₋₄ alkyl)(C₁₋₄ alkyl),
 - h) -CO₂H,
 - i) -CO₂(C₁₋₄ alkyl), and
 - j) -C₁₋₄ alkoxy;

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4) -C₁₋₄alkyl-phenyl, wherein the phenyl is either unsubstituted or substituted with one or two substituents selected from:

- 5
- a) -C₁₋₄ alkyl,
 - b) -halo,
 - c) -OH,
 - d) -CF₃,
 - e) -NH₂,
 - 10 f) -NH(C₁₋₄ alkyl),
 - g) -N(C₁₋₄ alkyl)₂,
 - h) -CO₂H,
 - i) -CO₂(C₁₋₄ alkyl), and
 - j) -C₁₋₄ alkoxy;

15 R¹_b is selected from the group consisting of:

- 1) R¹_a,
- 2) -C₃₋₇ cycloalkyl, and
- 3) -CH₂-R¹_a;

20 R²_a and R²_b are independently phenyl, either unsubstituted or substituted with one or two substituents selected from the group consisting of:

- 25
- 1) -C₁₋₄ alkoxy,
 - 2) -halo,
 - 3) -OH,
 - 4) -CF₃,
 - 5) -NH₂,
 - 6) -NH(C₁₋₄ alkyl),
 - 7) -N(C₁₋₄ alkyl)₂,
 - 8) -CO₂H,
 - 30 9) -CO₂(C₁₋₄ alkyl), and
 - 10) -C₁₋₆ alkyl, either unsubstituted or substituted with one or more substituents selected from the group consisting of:
 - a) -halo,
 - b) -OH,

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- 5
- c) -CF₃,
 - d) -NH₂,
 - e) -NH(C₁₋₄ alkyl),
 - f) -N(C₁₋₄ alkyl)(C₁₋₄ alkyl),
 - g) -CO₂H,
 - h) -CO₂(C₁₋₄ alkyl),
 - i) C₁₋₄alkoxy,
 - j) -S(O)_x(C₁₋₄ alkyl) wherein
10 x is 0, 1 or 2,
 - k) -C₃₋₇ cycloalkyl;

and the phenyl groups of R^{2a} and R^{2b} may be joined together at the ortho carbon atoms through a carbon-carbon single bond or C₁₋₃ alkylene to form a tricyclic group with the X² to which they are attached;

15 X¹ is -N, -CH or O, and if X¹ is O, R^{1a} is absent;

X² is -N or -CH;

20 R³ is selected from the group consisting of:

- 1) -CONR⁷R⁸, and
- 2) -CO₂R⁹;

25 R⁴, R⁵ and R⁶ are H or are independently selected from the definitions of R³;

R⁷ is C₁₋₆ alkyl substituted with one or more substituents selected from the group consisting of :

- 30
- 1) -NHR¹⁰,
 - 2) -NR¹⁰R¹¹,
 - 3) -NHCO(C₁₋₆ alkyl),
 - 4) -NR¹⁰CO₂R¹¹,
 - 5) -N(R¹⁰)((C₁₋₆ alkyl)CONHR¹¹),
 - 6) -N(CO₂R¹⁰)((C₁₋₆ alkyl)CONHR¹¹), and
 - 7) -NR¹⁰(C₁₋₆ alkyl)CONHR¹¹;

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R⁸ is H, C₁₋₆ alkyl or is independently selected from the definitions of R⁷;

5 R⁹ is H or -CH₂-phenyl, wherein the phenyl is either unsubstituted or substituted with one or more substituents selected from the group consisting of:

- 1) -C₁₋₄ alkoxy,
- 10 2) -halo,
- 3) -OH,
- 4) -CF₃,
- 5) -NH₂,
- 6) -NH(C₁₋₄ alkyl),
- 15 7) -N(C₁₋₄ alkyl)₂,
- 8) -CO₂H,
- 9) -CO₂(C₁₋₄ alkyl), and
- 20 10) -C₁₋₆ alkyl, either unsubstituted or substituted with one or more substituents selected from the group consisting of:
 - a) -halo,
 - b) -OH,
 - c) -CF₃,
 - d) -NH₂,
 - e) -NH(C₁₋₄ alkyl),
 - 25 f) -N(C₁₋₄ alkyl)(C₁₋₄ alkyl),
 - g) -CO₂H,
 - h) -CO₂(C₁₋₄ alkyl),
 - i) C₁₋₄alkoxy,
 - 30 j) -S(O)_x(C₁₋₄ alkyl) wherein
x is 0, 1 or 2,
 - k) -C₃₋₇ cycloalkyl;

R¹⁰ is H, C₁₋₆ alkyl, or -(C₁₋₆ alkyl)-phenyl, wherein the phenyl is either unsubstituted or substituted with one or more substituents selected from the group consisting of:

- 1) -C₁₋₄ alkoxy,

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- 5
- 2) -halo,
 - 3) -OH,
 - 4) -CF₃,
 - 5) -NH₂,
 - 6) -NH(C₁₋₄ alkyl),
 - 7) -N(C₁₋₄ alkyl)₂,
 - 8) -CO₂H,
 - 9) -CO₂(C₁₋₄ alkyl), and
 - 10) -C₁₋₆ alkyl, either unsubstituted or substituted with one or more substituents selected from the group consisting of:
 - a) -halo,
 - b) -OH,
 - c) -CF₃,
 - d) -NH₂,
 - e) -NH(C₁₋₄ alkyl),
 - f) -N(C₁₋₄ alkyl)(C₁₋₄ alkyl),
 - g) -CO₂H,
 - h) -CO₂(C₁₋₄ alkyl),
 - i) C₁₋₄alkoxy,
 - 20 j) -S(O)_x(C₁₋₄ alkyl) wherein x is 0, 1 or 2,
 - k) -C₃₋₇ cycloalkyl; and
- 15
- 20

25 R¹¹ is H, C₁₋₆ alkyl, or is independently selected from the definitions of R¹⁰.

The compounds of the present invention have asymmetric centers and this invention includes all of the optical isomers and mixtures thereof.

30 In addition compounds with carbon-carbon double bonds may occur in Z- and E- forms with all isomeric forms of the compounds being included in the present invention.

When any variable (e.g., alkyl, aryl, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, etc.) occurs more than one time in any variable or in

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Formula I, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "alkyl" includes those alkyl groups of a designated number of carbon atoms of either a straight, branched, or cyclic configuration. Examples of "alkyl" include methyl, ethyl, propyl, isopropyl, butyl, iso- sec- and tert-butyl, pentyl, hexyl, heptyl, 3-ethylbutyl, and the like. "Alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge, such as methoxy, ethoxy, propoxy, butoxy and pentoxy. "Alkenyl" is intended to include hydrocarbon chains of a specified number of carbon atoms of either a straight- or branched- configuration and at least one unsaturation, which may occur at any point along the chain, such as ethenyl, propenyl, butenyl, pentenyl, dimethylpentyl, and the like, and includes E and Z forms, where applicable. "Halogen" or "halo", as used herein, means fluoro, chloro, bromo and iodo.

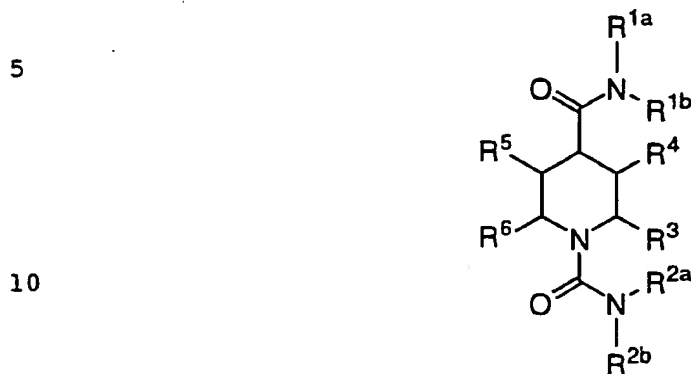
As will be understood by those skilled in the art, pharmaceutically acceptable salts include, but are not limited to salts with inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate or pamoate, salicylate and stearate. Similarly pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium and ammonium.

The term "aryl" means phenyl or naphthyl either unsubstituted or substituted with one, two or three substituents selected from the group consisting of halo, C₁-4-alkyl, C₁-4-alkoxy, NO₂, CF₃, C₁-4-alkylthio, OH, -N(R⁶)₂, -CO₂R⁶, C₁-4-polyfluoroalkyl, C₃-6-polyfluorocycloalkyl, and tetrazol-5-yl.

The term "heteroaryl" means an unsubstituted, mono-substituted or disubstituted five or six membered aromatic heterocycle comprising from 1 to 3 heteroatoms selected from the group consisting of O, N and S and wherein the substituents are members selected from the group consisting of -OH, -SH, -C₁-4-alkyl, -C₁-4-alkoxy, -CF₃, halo, -NO₂, -CO₂R⁶, -N(R⁶)₂ and a fused benzo group.

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One embodiment of the novel compounds of this invention is that wherein X¹ and X² are both N of structural formula:



15 or a pharmaceutically acceptable salt thereof.

A first class of compounds within this embodiment are those compounds wherein:

20 R^{1a} is selected from the group consisting of:

- 1) H,
- 2) C₁₋₈ alkyl,
- 3) phenyl, either unsubstituted or substituted with one or two substituents selected from the group consisting of:
 - 25 a) -C₁₋₄ alkyl,
 - b) -halo,
 - c) -OH,
 - d) -CF₃,
 - e) -NH₂,
 - 30 f) -NH(C₁₋₄ alkyl),
 - g) -N(C₁₋₄ alkyl)(C₁₋₄ alkyl),
 - h) -CO₂H,
 - i) -CO₂(C₁₋₄ alkyl), and
 - j) -C₁₋₄ alkoxy;

- 15 -

4) -C₁₋₄alkyl-phenyl, wherein the phenyl is either unsubstituted or substituted with one or two substituents selected from:

- 5
- a) -C₁₋₄ alkyl,
 - b) -halo,
 - e) -OH,
 - d) -CF₃,
 - e) -NH₂,
 - 10 f) -NH(C₁₋₄ alkyl),
 - g) -N(C₁₋₄ alkyl)₂,
 - h) -CO₂H,
 - i) -CO₂(C₁₋₄ alkyl), and
 - j) -C₁₋₄ alkoxy;

15 R_{1b} is selected from the group consisting of:

- 1) R_{1a},
- 2) -C₃₋₇ cycloalkyl, and
- 3) -CH₂-R_{1a};

20 R_{2a} and R_{2b} are independently phenyl, either unsubstituted or substituted with one or two substituents selected from the group consisting of:

- 25
- 1) -C₁₋₄ alkoxy,
 - 2) -halo,
 - 3) -OH,
 - 4) -CF₃,
 - 5) -NH₂,
 - 6) -NH(C₁₋₄ alkyl),
 - 7) -N(C₁₋₄ alkyl)₂,
 - 8) -CO₂H,
 - 30 9) -CO₂(C₁₋₄ alkyl), and
 - 10) -C₁₋₆ alkyl, either unsubstituted or substituted with one or more substituents selected from the group consisting of:
- a) -halo,
 - b) -OH,

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- 5
- c) -CF₃,
 - d) -NH₂,
 - e) -NH(C₁₋₄ alkyl),
 - f) -N(C₁₋₄ alkyl)(C₁₋₄ alkyl),
 - g) -CO₂H,
 - h) -CO₂(C₁₋₄ alkyl),
 - i) C₁₋₄alkoxy,
 - j) -S(O)_x(C₁₋₄ alkyl) wherein
 - 10 x is 0, 1 or 2, and
 - k) -C₃₋₇ cycloalkyl;

and the phenyl groups of R^{2a} and R^{2b} may be joined together at the ortho carbon atoms through a carbon-carbon single bond or C₁₋₃ alkylene to form a tricyclic group with the X² to which they are attached;

15 R³ is -CONR⁷R⁸;

R⁴, R⁵ and R⁶ are H;

20 R⁷ is C₁₋₆ alkyl substituted with one or more substituents selected from the group consisting of :

- 1) -N(R¹⁰)(CH₂CONHR¹¹),
- 2) -N(CO₂R¹⁰)(CH₂CONHR¹¹), and

25 R⁸ is H.

Specific compounds within this first class include:

- 1) trans 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(2-(N-(amino-carbonylmethyl)amino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine;
- 30 2) trans 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(2-(N-(2-methoxy-benzyl)-(N-(aminocarbonylmethyl)amino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine;

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- 3) trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-2-(RS)-(2-(N-(benzyloxycarbonyl)-N-(aminocarbonylmethyl)amino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)-piperidine;
- 4) trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-2-(RS)-(2-N-(aminocarbonylmethyl)amino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine;
- 5) trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-(N-aminocarbonylmethyl)amino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine; or a pharmaceutically acceptable salt thereof.

A second class of compounds within this embodiment are those compounds wherein:

R^{1a} is selected from the group consisting of:

- 1) H,
- 2) C₁₋₈ alkyl,
- 3) phenyl, either unsubstituted or substituted with one or two substituents selected from the group consisting of:
 - a) -C₁₋₄ alkyl,
 - b) -halo,
 - c) -OH,
 - d) -CF₃,
 - e) -NH₂,
 - f) -NH(C₁₋₄ alkyl),
 - g) -N(C₁₋₄ alkyl)(C₁₋₄ alkyl),
 - h) -CO₂H,
 - i) -CO₂(C₁₋₄ alkyl), and
 - j) -C₁₋₄ alkoxy;

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- 4) -C₁₋₄alkyl-phenyl, wherein the phenyl is either unsubstituted or substituted with one or two substituents selected from:
- a) -C₁₋₄ alkyl,
 - b) -halo,
 - c) -OH,
 - d) -CF₃,
 - e) -NH₂,
 - f) -NH(C₁₋₄ alkyl),
 - g) -N(C₁₋₄ alkyl)₂,
 - h) -CO₂H,
 - i) -CO₂(C₁₋₄ alkyl), and
 - j) -C₁₋₄ alkoxy;
- 15 R1b is selected from the group consisting of:
- 1) R1a,
 - 2) -C₃₋₇ cycloalkyl, and
 - 3) -CH₂-R1a;
- 20 R2a and R2b are independently phenyl, either unsubstituted or substituted with one or two substituents selected from the group consisting of:
- 1) -C₁₋₄ alkoxy,
 - 2) -halo,
 - 3) -OH,
 - 4) -CF₃,
 - 5) -NH₂,
 - 6) -NH(C₁₋₄ alkyl),
 - 7) -N(C₁₋₄ alkyl)₂,
 - 8) -CO₂H,
 - 9) -CO₂(C₁₋₄ alkyl), and
 - 10) -C₁₋₆ alkyl, either unsubstituted or substituted with one or more substituents selected from the group consisting of:
- a) -halo,
 - b) -OH,

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- 5 c) -CF₃,
 d) -NH₂,
 e) -NH(C₁₋₄ alkyl),
 f) -N(C₁₋₄ alkyl)(C₁₋₄ alkyl),
 g) -CO₂H,
 h) -CO₂(C₁₋₄ alkyl),
 i) C₁₋₄alkoxy,
 j) -S(O)_x(C₁₋₄ alkyl) wherein
 x is 0, 1 or 2,
 10 k) -C₃₋₇ cycloalkyl;

and the phenyl groups of R^{2a} and R^{2b} may be joined together at the ortho carbon atoms through a carbon-carbon single bond or C₁₋₃ alkylene to form a tricyclic group with the X² to which they are attached;

15 R³ is -CONR⁷R⁸;

R⁴, R⁵ and R⁶ are H;

20 R⁷ is C₁₋₆ alkyl substituted with -NR¹⁰R¹¹;

R⁸ is H;

R¹⁰ is -(C₁₋₆ alkyl)-phenyl, wherein the phenyl is substituted with -C₁₋₄ alkoxy,

25 R¹¹ is H, C₁₋₆ alkyl, or is independently selected from the definitions of R¹⁰.

Specific compounds within this second class include:

- 30 1) trans 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methylamino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine;

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- 2) cis 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methylamino)ethylaminocarbonyl)-4-(SR)-(N,N-dipentylaminocarbonyl)piperidine;
- 5 3) trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methylamino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine;
- 10 4) trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methylamino)ethylaminocarbonyl)-4-(RS)-(N,N-dibenzylaminocarbonyl)piperidine;

or a pharmaceutically acceptable salt thereof.

- 15 A third class of compounds within this embodiment are those compounds wherein:

R1a is selected from the group consisting of:

- 20 1) H,
2) C₁₋₈ alkyl,
3) phenyl, either unsubstituted or substituted with one or two substituents selected from the group consisting of:
- 25 a) -C₁₋₄ alkyl,
b) -halo,
c) -OH,
d) -CF₃,
e) -NH₂,
f) -NH(C₁₋₄ alkyl),
g) -N(C₁₋₄ alkyl)(C₁₋₄ alkyl),
30 h) -CO₂H,
i) -CO₂(C₁₋₄ alkyl), and
j) -C₁₋₄ alkoxy;

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- 4) -C₁₋₄alkyl-phenyl, wherein the phenyl is either unsubstituted or substituted with one or two substituents selected from:

- 5 a) -C₁₋₄ alkyl,
b) -halo,
c) -OH,
d) -CF₃,
e) -NH₂,
10 f) -NH(C₁₋₄ alkyl),
g) -N(C₁₋₄ alkyl)₂,
h) -CO₂H,
i) -CO₂(C₁₋₄ alkyl), and
j) -C₁₋₄ alkoxy;

15 R1b is selected from the group consisting of:

- 1) R1a,
2) -C₃₋₇ cycloalkyl, and
3) -CH₂-R1a;

20 R2a and R2b are independently phenyl, either unsubstituted or substituted with one or two substituents selected from the group consisting of:

- 25 1) -C₁₋₄ alkoxy,
2) -halo,
3) -OH,
4) -CF₃,
5) -NH₂,
6) -NH(C₁₋₄ alkyl),
7) -N(C₁₋₄ alkyl)₂,
8) -CO₂H,
30 9) -CO₂(C₁₋₄ alkyl), and
10) -C₁₋₆ alkyl, either unsubstituted or substituted with one or more substituents selected from the group consisting of:
a) -halo,
b) -OH,

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- 5
- c) -CF₃,
 - d) -NH₂,
 - e) -NH(C₁₋₄ alkyl),
 - f) -N(C₁₋₄ alkyl)(C₁₋₄ alkyl),
 - g) -CO₂H,
 - h) -CO₂(C₁₋₄ alkyl),
 - i) C₁₋₄alkoxy,
 - j) -S(O)_x(C₁₋₄ alkyl) wherein
x is 0, 1 or 2,
 - 10 k) -C₃₋₇ cycloalkyl;

and the phenyl groups of R^{2a} and R^{2b} may be joined together at the ortho carbon atoms through a carbon-carbon single bond or C₁₋₃ alkylene to form a tricyclic group with the X² to which they are attached;

15 R³ is CONR⁷R⁸;

R⁴, R⁵ and R⁶ are H;

20 R⁷ is C₁₋₆ alkyl substituted with -NR¹⁰R¹¹;

R⁸ is H;

R¹⁰ is C₁₋₆ alkyl;

25 R¹¹ is H or C₁₋₆ alkyl.

Specific compounds within this third class include:

- 30 1) trans 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(3-(diethylamino)-propylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)-piperidine;

or a pharmaceutically acceptable salt thereof.

A fourth class of compounds within this embodiment are those compounds wherein:

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R1a is selected from the group consisting of:

- 1) H,
- 2) C₁-8 alkyl,
- 3) phenyl, either unsubstituted or substituted with one or two substituents selected from the group consisting of:
 - a) -C₁-4 alkyl,
 - b) -halo,
 - c) -OH,
 - d) -CF₃,
 - e) -NH₂,
 - f) -NH(C₁-4 alkyl),
 - g) -N(C₁-4 alkyl)(C₁-4 alkyl),
 - h) -CO₂H,
 - i) -CO₂(C₁-4 alkyl), and
 - j) -C₁-4 alkoxy;
- 4) -C₁-4alkyl-phenyl, wherein the phenyl is either unsubstituted or substituted with one or two substituents selected from:
 - a) -C₁-4 alkyl,
 - b) -halo,
 - c) -OH,
 - d) -CF₃,
 - e) -NH₂,
 - f) -NH(C₁-4 alkyl),
 - g) -N(C₁-4 alkyl)₂,
 - h) -CO₂H,
 - i) -CO₂(C₁-4 alkyl), and
 - j) -C₁-4 alkoxy;

R1b is selected from the group consisting of:

- 1) R1a,
- 2) -C₃-7 cycloalkyl, and

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3) -CH₂-R^{1a};

R^{2a} and R^{2b} are independently phenyl, either unsubstituted or substituted with one or two substituents selected from the group consisting of:

- 5 1) -C₁₋₄ alkoxy,
 2) -halo,
 3) -OH,
 4) -CF₃,
 5) -NH₂,
10 6) -NH(C₁₋₄ alkyl),
 7) -N(C₁₋₄ alkyl)₂,
 8) -CO₂H,
 9) -CO₂(C₁₋₄ alkyl), and
15 10) -C₁₋₆ alkyl, either unsubstituted or substituted with one or
 more substituents selected from the group consisting of:
 a) -halo,
 b) -OH,
 c) -CF₃,
 d) -NH₂,
20 e) -NH(C₁₋₄ alkyl),
 f) -N(C₁₋₄ alkyl)(C₁₋₄ alkyl),
 g) -CO₂H,
 h) -CO₂(C₁₋₄ alkyl),
 i) C₁₋₄alkoxy,
25 j) -S(O)_x(C₁₋₄ alkyl) wherein
 x is 0, 1 or 2,
 k) -C₃₋₇ cycloalkyl;

and the phenyl groups of R^{2a} and R^{2b} may be joined together at the ortho carbon atoms through a carbon-carbon single bond or C₁₋₃ alkylene to form a tricyclic group with the X² to which they are attached;

R³ is -CO₂R⁹;

R⁴, R⁵ and R⁶ are H;

- 25 -

R⁹ is H.

Specific compounds within this fourth class include:

5

1) trans 1-(N,N-diphenylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine-2-(RS)-carboxylic acid;

10

2) trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine-2-(RS)-carboxylic acid;

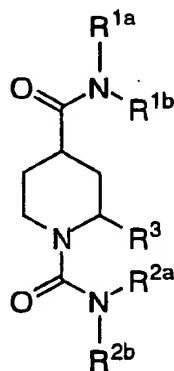
or a pharmaceutically acceptable salt thereof.

15

Especially preferred compounds include those of structural

Formula II:

20



25

II

or a pharmaceutically acceptable salt thereof, wherein:

30

R^{1a} is selected from the group consisting of:

- 1) C5-6 alkyl,
- 2) phenyl,
- 3) -CH₂-phenyl,

R^{1b} is selected from the definitions of R^{1a};

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R^{2a} and R^{2b} are independently phenyl, either unsubstituted or substituted with one substituent selected from the group consisting of:

- 5
- 1) -OCH₃,
 - 2) -Cl,
 - 3) -CF₃,
 - 4) -CH₃;

10 R³ is selected from the group consisting of:

- 1) -CONR⁷R⁸, and
- 2) -CO₂R⁹;

R⁷ is C₁₋₆ alkyl substituted with one or more substituents selected from the group consisting of:

- 15
- 1) -NHR¹⁰,
 - 2) -NR¹⁰R¹¹,
 - 3) -NHCO (C₁₋₆ alkyl),
 - 4) -NR¹⁰CO₂R¹¹,
 - 5) -N(CO₂R¹⁰)((C₁₋₆ alkyl)CONHR¹¹),
 - 20 6) -NR¹⁰(C₁₋₆ alkyl)CONHR¹¹;

R⁸ is H, C₁₋₆ alkyl or is independently selected from the definitions of R⁷;

25 R⁹ is H or -CH₂-phenyl, wherein the phenyl is either unsubstituted or substituted with one or more substituents selected from the group consisting of:

- 30
- 1) -C₁₋₄ alkoxy,
 - 2) -halo,
 - 3) -OH,
 - 4) -CF₃,
 - 5) -NH₂,
 - 6) -NH(C₁₋₄ alkyl),
 - 7) -N(C₁₋₄ alkyl)₂,
 - 8) -CO₂H,

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- 9). -CO₂(C₁₋₄ alkyl), and
10) -C₁₋₆ alkyl, either unsubstituted or substituted with one or more substituents selected from the group consisting of:
- 5 a) -halo,
 - b) -OH,
 - c) -CF₃,
 - d) -NH₂,
 - e) -NH(C₁₋₄ alkyl),
 - 10 f) -N(C₁₋₄ alkyl)(C₁₋₄ alkyl),
 - g) -CO₂H,
 - h) -CO₂(C₁₋₄ alkyl),
 - i) C₁₋₄alkoxy,
 - j) -S(O)_x(C₁₋₄ alkyl) wherein
15 x is 0, 1 or 2,
 - k) -C₃₋₇ cycloalkyl;

- R₁₀ is -(C₁₋₄ alkyl)-phenyl, wherein the phenyl is either unsubstituted or substituted with one or more substituents selected from the group consisting of:
- 20 1) -OCH₃,
 - 2) -Cl,
 - 3) -CF₃,
 - 4) -CH₃; and

- 25 R₁₁ is H, C₁₋₆ alkyl, or is independently selected from the definitions of R₁₀.

30 The useful activities of the compounds of this invention are demonstrated and exemplified by the following assays.

TACHYKININ ANTAGONISM ASSAY

The compounds of this invention are useful for antagonizing tachykinins, in particular substance P and neurokinin A in the treatment

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of gastrointestinal disorders, central nervous system disorders, inflammatory diseases, pain or migraine and asthma in a mammal in need of such treatment. This activity can be demonstrated by the following assay.

5

A. Receptor Expression in COS

To express the cloned human neurokinin-1 receptor (NK1R) transiently in COS, the cDNA for the human NK1R was cloned into the expression vector pCDM9 which was derived from pCDM8
10 (INVITROGEN) by inserting the ampicillin resistance gene (nucleotide 1973 to 2964 from BLUESCRIPT SK+) into the Sac II site. Transfection of 20 ug of the plasmid DNA into 10 million COS cells was achieved by electroporation in 800 ul of transfection buffer (135 mM NaCl, 1.2 mM CaCl₂, 1.2 mM MgCl₂, 2.4 mM K₂HPO₄, 0.6 mM KH₂PO₄, 10 mM
15 glucose, 10 mM HEPES pH 7.4) at 260 V and 950 uF using the IBI GENEZAPPER (IBI, New Haven, CT). The cells were incubated in 10% fetal calf serum, 2 mM glutamine, 100U/ml penicillin-streptomycin, and 90% DMEM media (GIBCO, Grand Island, NY) in 5% CO₂ at 37°C for three days before the binding assay.
20

B. Stable Expression in CHO

To establish a stable cell line expressing the cloned human NK1R, the cDNA was subcloned into the vector pRcCMV
25 (INVITROGEN). Transfection of 20 ug of the plasmid DNA into CHO cells was achieved by electroporation in 800 ul of transfection buffer supplemented with 0.625 mg/ml Herring sperm DNA at 300 V and 950 uF using the IBI GENEZAPPER (IBI). The transfected cells were incubated in CHO media [10 % fetal calf serum, 100 U/ml penicillin-streptomycin, 2 mM glutamine, 1/500 hypoxanthine-thymidine (ATCC),
30 90% IMDM media (JRH BIOSCIENCES, Lenexa, KS), 0.7 mg/ml G418 (GIBCO)] in 5% CO₂ at 37°C until colonies were visible. Each colony was separated and propagated. The cell clone with the highest number of human NK1R was selected for subsequent applications such as drug screening.

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C. Assay Protocol using COS or CHO

10 The binding assay of human NK1R expressed in either COS
or CHO cells is based on the use of ^{125}I -substance P (^{125}I -SP, from DU
5 PONT, Boston, MA) as a radioactively labeled ligand which competes
with unlabeled substance P or any other ligand for binding to the human
NK1R. Monolayer cell cultures of COS or CHO were dissociated by the
non-enzymatic solution (SPECIALTY MEDIA, Lavallette, NJ) and
10 resuspended in appropriate volume of the binding buffer (50 mM Tris pH
7.5, 5 mM MnCl_2 , 150 mM NaCl, 0.04 mg/ml bacitracin, 0.004 mg/ml
leupeptin, 0.2 mg/ml BSA, 0.01 mM phosphor-amidon) such that 200 μl
of the cell suspension would give rise to about 10,000 cpm of specific
 ^{125}I -SP binding (approximately 50,000 to 200,000 cells). In the binding
15 assay, 200 μl of cells were added to a tube containing 20 μl of 1.5 to 2.5
nM of ^{125}I -SP and 20 μl of unlabeled substance P or any other test
compound. The tubes were incubated at 4°C or at room temperature for
1 hour with gentle shaking. The bound radioactivity was separated from
unbound radioactivity by GF/C filter (BRANDEL, Gaithersburg, MD)
20 which was pre-wetted with 0.1 % polyethylenimine. The filter was
washed with 3 ml of wash buffer (50 mM Tris pH 7.5, 5 mM MnCl_2 , 150
mM NaCl) three times and its radioactivity was determined by gamma
counter.

The activation of phospholipase C by NK1R may also be
25 measured in CHO cells expressing the human NK1R by determining the
accumulation of inositol monophosphate which is a degradation product
of IP_3 . CHO cells are seeded in 12-well plate at 250,000 cells per well.
After incubating in CHO media for 4 days, cells are loaded with 0.025
 $\mu\text{Ci/ml}$ of ^3H -myoinositol by overnight incubation. The extracellular
radioactivity is removed by washing with phosphate buffered saline.
30 LiCl is added to the well at final concentration of 0.1 mM with or without
the test compound, and incubation is continued at 37°C for 15 min.
Substance P is added to the well at final concentration of 0.3 nM to
activate the human NK1R. After 30 min of incubation at 37°C , the media
is removed and 0.1 N HCl is added. Each well is sonicated at 4°C and

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extracted with CHCl_3 /methanol (1:1). The aqueous phase is applied to a 1 ml Dowex AG 1X8 ion exchange column. The column is washed with 0.1 N formic acid followed by 0.025 M ammonium formate-0.1 N formic acid. The inositol monophosphate is eluted with 0.2 M ammonium formate-0.1 N formic acid and quantitated by beta counter.

The compounds of the present invention are useful in the prevention and treatment of a wide variety of clinical conditions which are characterized by the presence of an excess of tachykinin, in particular substance P, activity.

These conditions may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as AIDS related dementia, senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) and other neuropathological disorders such as peripheral neuropathy, for example AIDS related neuropathy, diabetic neuropathy, chemotherapy-induced neuropathy, and postherpetic and other neuralgias; respiratory diseases such as chronic obstructive airways disease, bronchopneumonia, chronic bronchitis, bronchospasm and asthma; airways disease modulated by neurogenic inflammation; diseases characterized by neurogenic mucus secretion, such as cystic fibrosis; diseases associated with decreased glandular secretions, including lacrimation, such as Sjogren's syndrome, hyperlipoproteinemias IV and V, hemochromatosis, sarcoidosis, or amyloidosis; inflammatory diseases such as inflammatory bowel disease, irritable bowel syndrome, psoriasis, fibrositis, ocular inflammation, osteoarthritis and rheumatoid arthritis; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, dry eye syndrome, and the like; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis; oedema, such as oedema caused by thermal injury; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; adverse immunological

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reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression, such as systemic lupus erythematosus; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease and incontinence; emesis, including acute, delayed, post-operative, late-phase, and anticipatory emesis, for example, induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorder, motion, post-operative sickness, surgery, gastrointestinal obstruction, reduced gastrointestinal motility, visceral pain, migraine, opioid analgesics and variations in intracranial pressure (except quaternary salts); disorders of bladder function such as bladder detrusor hyperreflexia; fibrosing and collagen diseases such as scleroderma and eosinophilic fasciitis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease; and pain or nociception, for example, chronic pain or that attributable to or associated with any of the foregoing conditions especially the transmission of pain in migraine. Hence, these compounds may be readily adapted to therapeutic use for the treatment of physiological disorders associated with an excessive stimulation of tachykinin receptors, especially neurokinin-1, and as neurokinin-1 antagonists in the control and/or treatment of any of the aforesaid clinical conditions in mammals, including humans.

For example, the compounds of the present invention may suitably be used in the prevention or treatment of disorders of the central nervous system such as anxiety, psychosis and schizophrenia; neurodegenerative disorders such as senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, broncho-pneumonia, chronic bronchitis, cystic fibrosis and asthma, and bronchospasm; inflammatory diseases such as inflammatory bowel disease, osteoarthritis and rheumatoid arthritis; adverse immunological reactions such as rejection of transplanted tissues; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera

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5 such as ulcerative colitis, Crohn's disease and incontinence; disorders of blood flow caused by vasodilation; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions or the transmission of pain in migraine (both prophylaxis and acute treatment).

10 As calcium channel blocking agents some of the compounds of the present invention are useful in the prevention of treatment of clinical conditions which benefit from inhibition of the transfer of calcium ions across the plasma membrane of cells. These include diseases and disorders of the heart and vascular system such as angina pectoris, myocardial infarction, cardiac arrhythmia, cardiac hypertrophy, cardiac vasospasm, hypertension, cerebrovascular spasm and other ischemic disease. Furthermore, these compounds may be capable of lowering elevated intraocular pressure when administered topically to the hypertensive eye in solution in a suitable ophthalmic vehicle. Also, these compounds may be useful in the reversal of multidrug resistance in tumor cells by enhancing the efficacy of chemotherapeutic agents. In addition, these compounds may have activity in blocking calcium channels in insect brain membranes and so may be useful as insecticides.

20 The compounds of the present invention are particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example: neuropathy, such as diabetic or peripheral neuropathy and chemotherapy-induced neuropathy; postherpetic and other neuralgias; asthma; osteoarthritis; rheumatoid arthritis; and especially migraine. The compounds of the present invention are also particularly useful in the treatment of diseases characterized by neurogenic mucus secretion, especially cystic fibrosis.

30 In the treatment of the clinical conditions noted above, the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

The pharmaceutical compositions of this invention can be used in the form of a pharmaceutical preparation, for example, in solid,

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semisolid or liquid form, which contains one or more of the compounds of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the disease.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g., conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g., water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an

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enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solution, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

For the treatment of the clinical conditions and diseases noted above, the compounds of this invention may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used

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herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

5 For the treatment of certain conditions it may be desirable to employ a compound of the present invention in conjunction with another pharmacologically active agent. For example, for the treatment of respiratory diseases such as asthma, a compound of the present invention may be used in conjunction with a bronchodilator, such as a β 2-
10 adrenergic receptor agonist or tachykinin antagonist which acts at neurokinin-2 receptors. Also, for the treatment of conditions that require antagonism of both neurokinin-1 and neurokinin-2, including disorders associated with bronchoconstriction and/or plasma extravasation in airways, such as asthma, chronic bronchitis, airways disease, or cystic fibrosis, a compound of the present invention may be used in conjunction
15 with a tachykinin antagonist which acts at neurokinin-2 receptors, or with tachykinin receptor antagonist which acts at both neurokinin-1 and neurokinin-2 receptors. Similarly, for the prevention or treatment of emesis a compound of the present invention may be used in conjunction with other anti-emetic agents, especially 5HT₃ receptor antagonists, such
20 as ondansetron, granisetron, tropisetron, decadron, and zatisetron. Likewise, for the prevention or treatment of migraine a compound of the present invention may be used in conjunction with other anti-migraine agents, such as ergotamines or 5HT₁ agonists, especially sumatriptan. For the prevention or treatment of inflammatory conditions in the lower urinary tract, especially cystitis, a compound of the present invention may
25 be used in conjunction with an antiinflammatory, such as a bradykinin receptor antagonist. The compound of the present invention and the other pharmacologically active agent may be administered to a patient simultaneously, sequentially or in combination.

30 The compounds of this invention may be administered to patients (animals and human) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. The dose will vary from patient to patient depending upon the nature and severity of disease, the patient's weight, special diets then being followed by a patient,

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concurrent medication, and other factors which those skilled in the art will recognize.

5 In the treatment of a condition associated with an excess of tachykinins, an appropriate dosage level will generally be about 0.001 to 50 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.005 to about 25 mg/kg per day; more preferably about 0.01 to about 10 mg/kg per day; and even more preferably about 0.05 to about 1 mg/kg per day. For example, in the treatment of conditions involving the

10 neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.01 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or

15 twice per day.

Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples wherein R1, R2, R3, R4, R5, R6, R7, R8, R9, R10 and R11 are as defined above.

20 ABBREVIATIONS USED IN SCHEMES AND EXAMPLES

TABLE 1

Reagents:

25	Et ₃ N	triethylamine
	Ph ₃ P	triphenylphosphine
	TFA	trifluoroacetic acid
	NaOEt	sodium ethoxide
	DCC	N,N'-dicyclohexylcarbodiimide
30	DCU	N,N'-dicyclohexylurea
	CDI	1,1'-carbonyldiimidazole
	MCPBA	m-chloroperbenzoic acid
	DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
	Cbz-Cl	benzyl chloroformate

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	ACE-Cl	alpha-chloroethyl chloroformate
	iPr ₂ NEt or DIEA	N,N-diisopropylethylamine
	NHS	N-hydroxysuccinimide
	DIBAL	diisobutylaluminum hydride
5	Me ₂ SO ₄	dimethyl sulfate
	HOBt	1-hydroxybenzotriazole hydrate
	EDAC	1-ethyl-3-(3-dimethylaminopropyl)carbo- diimide
	hydrochloride	

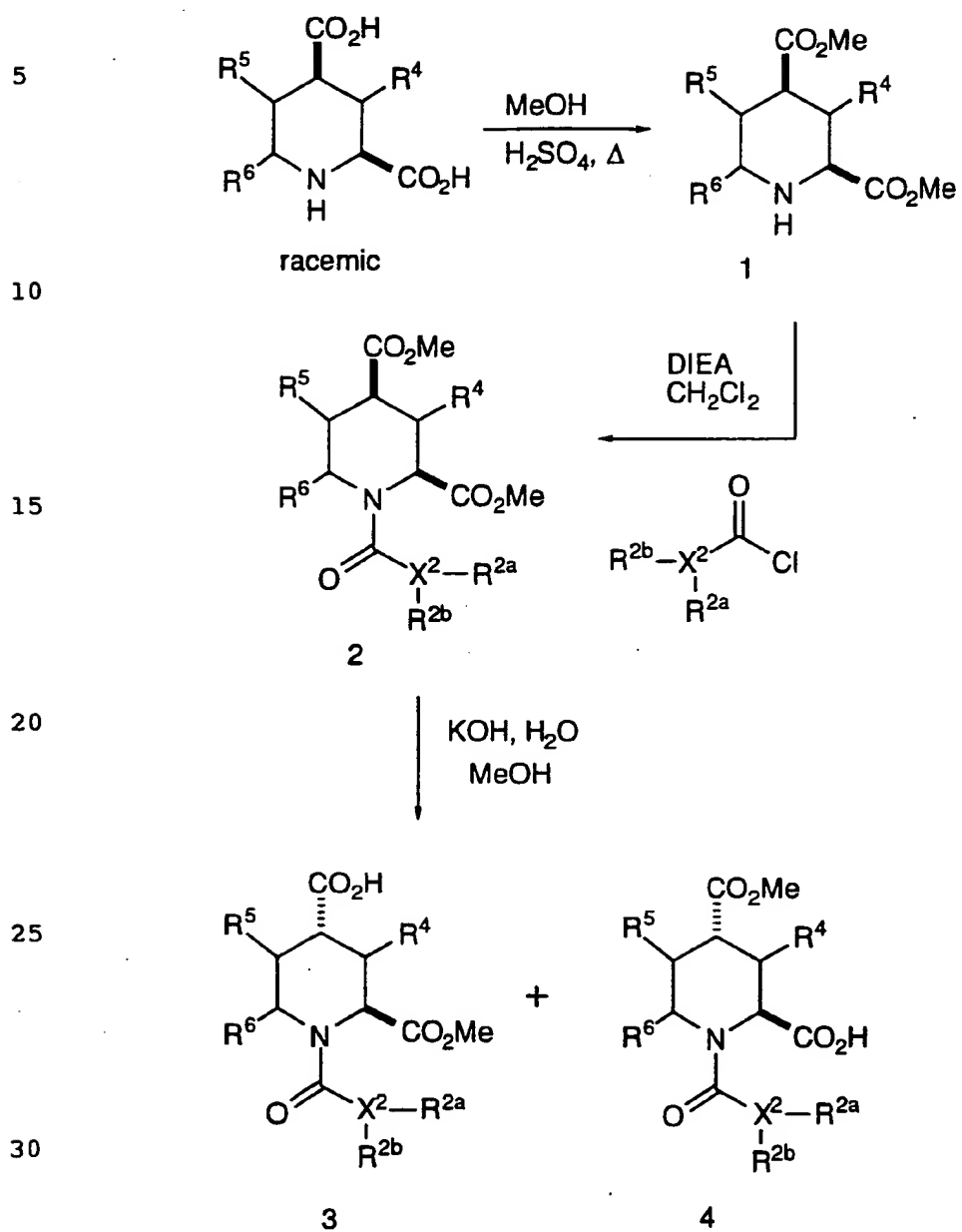
10 Solvents:

	DMF	dimethylformamide
	THF	tetrahydrofuran
	MeOH	methanol
15	EtOH	ethanol
	AmOH	n-amyl alcohol
	AcOH	acetic acid
	MeCN	acetonitrile
20	DMSO	dimethylsulfoxide

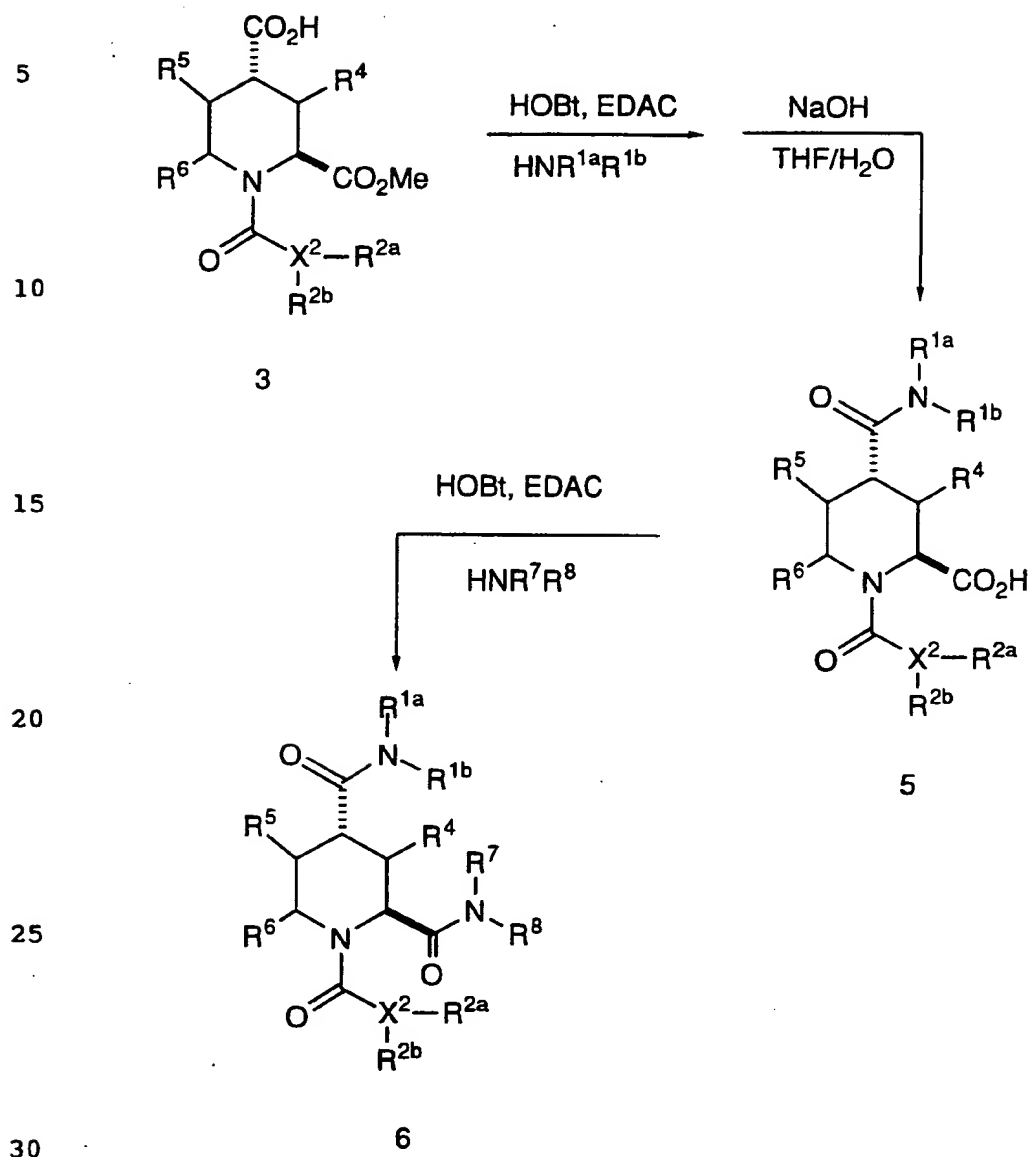
Others:

	Ph	phenyl
	Ar	aryl
25	Me	methyl
	Et	ethyl
	iPr	isopropyl
	Am	n-amyl
	Cbz	carbobenzyloxy (benzyloxy-carbonyl)
30	BOC	<u>tert</u> -butoxycarbonyl
	PTC	phase transfer catalyst
	cat.	catalytic
	FAB-MS	fast atom bombardment mass spectrometry
	rt	room temperature

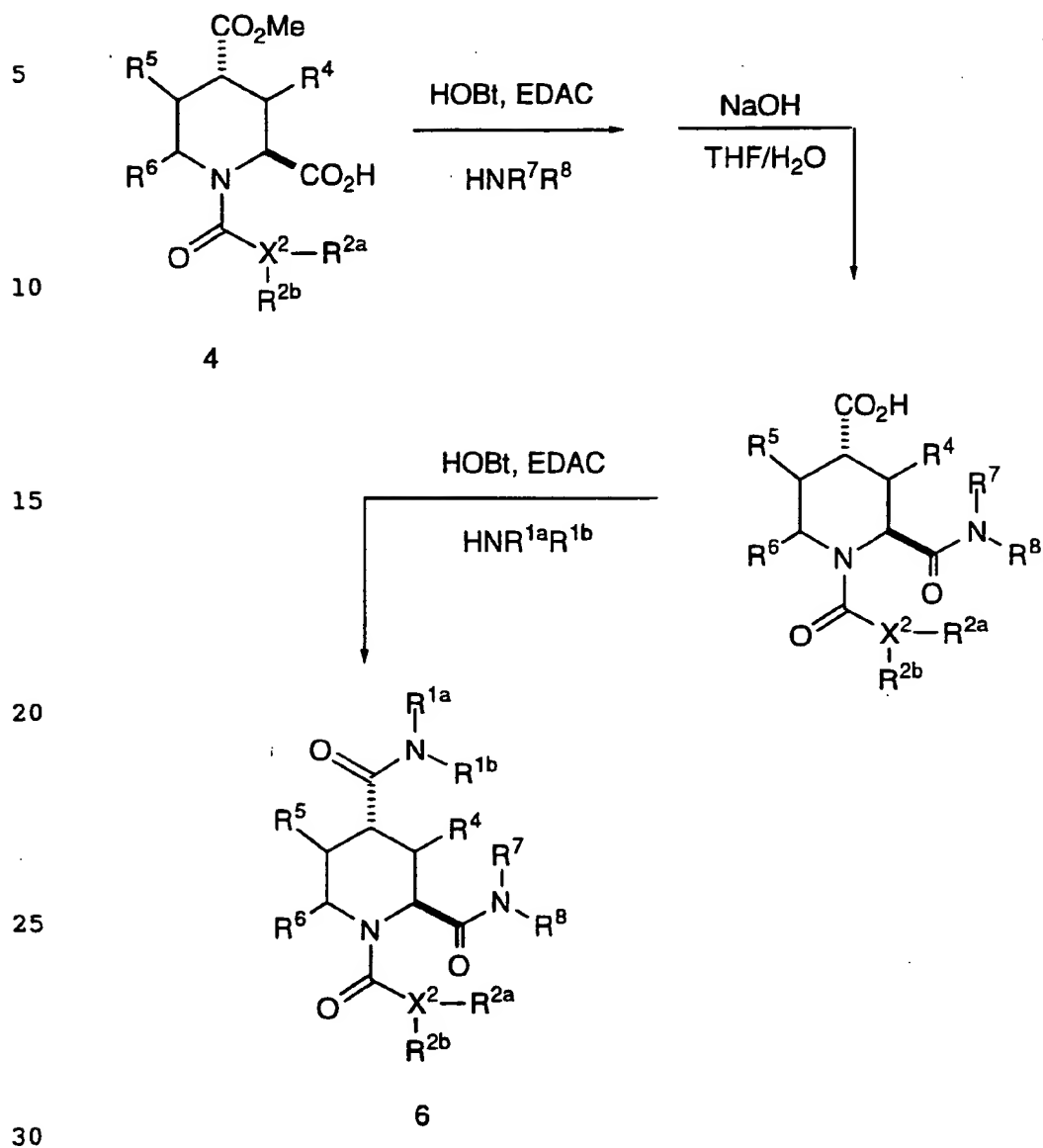
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SCHEME 1

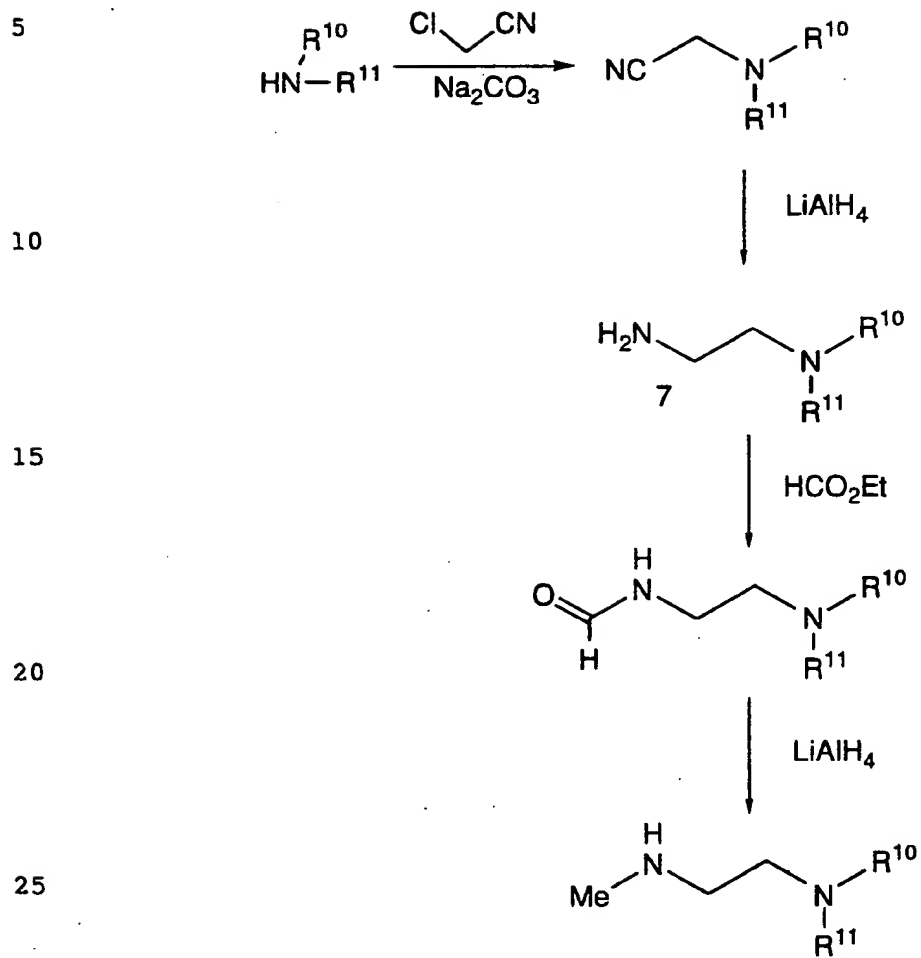
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SCHEME 2

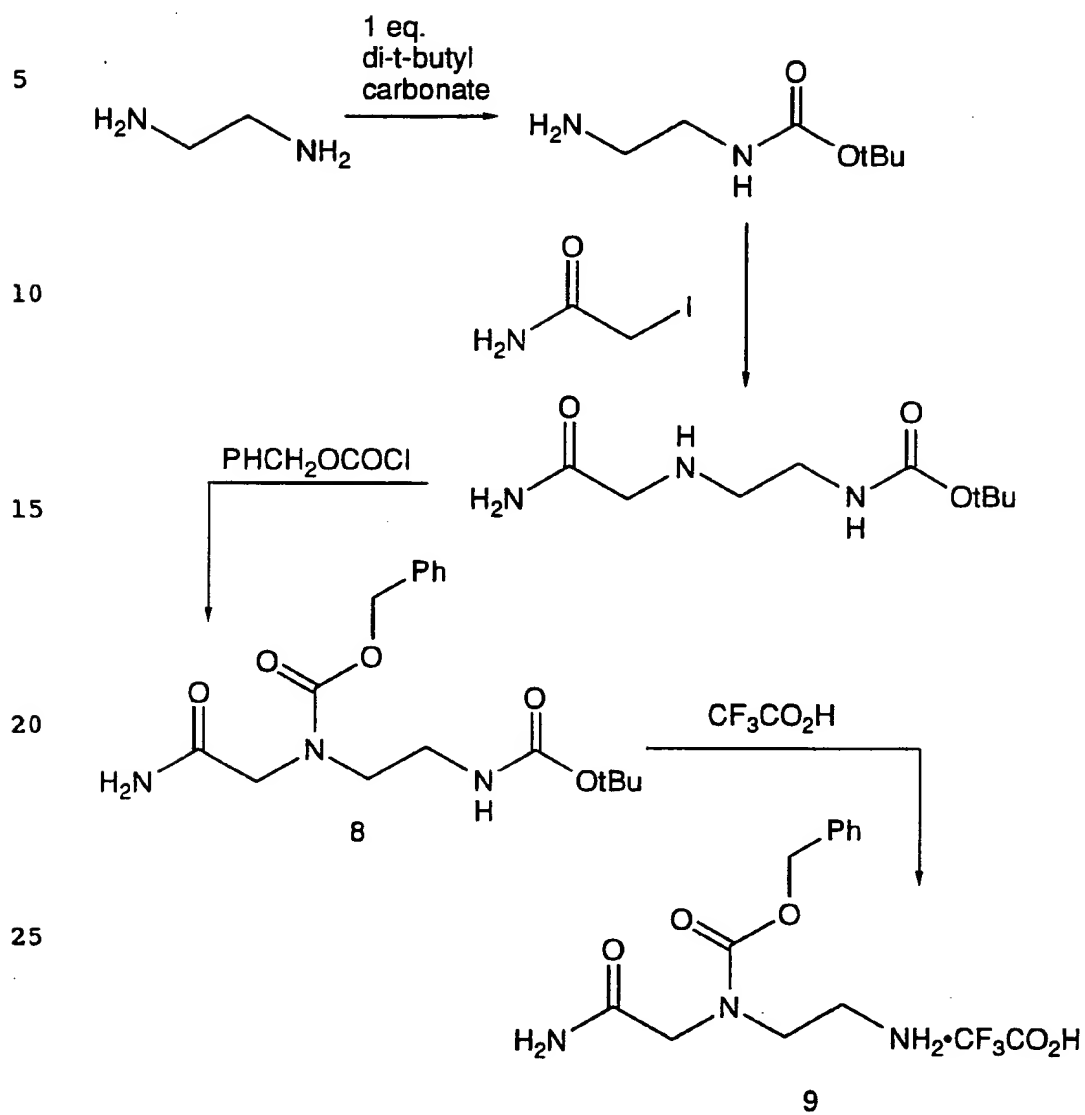
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SCHEME 3

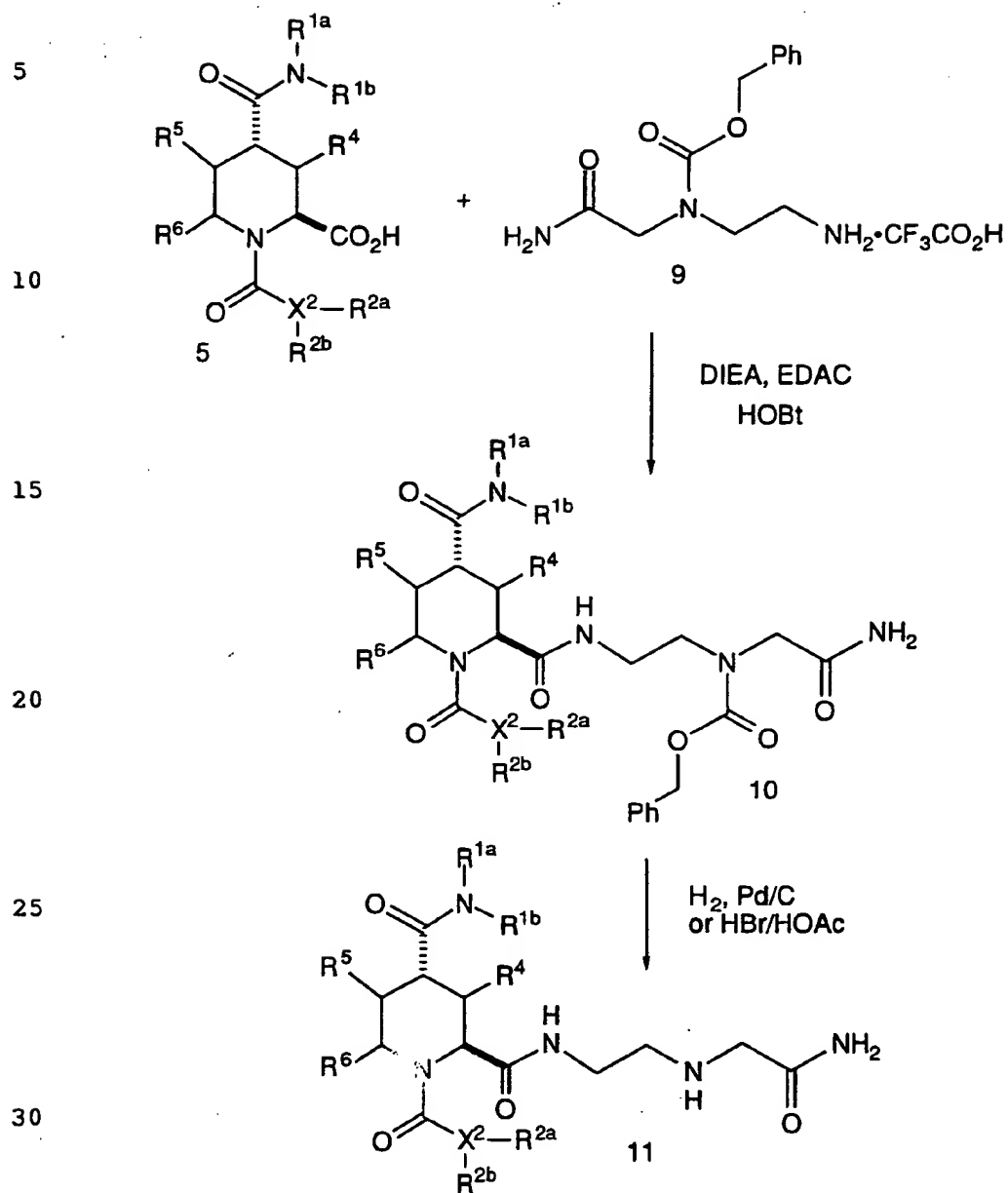
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SCHEME 4

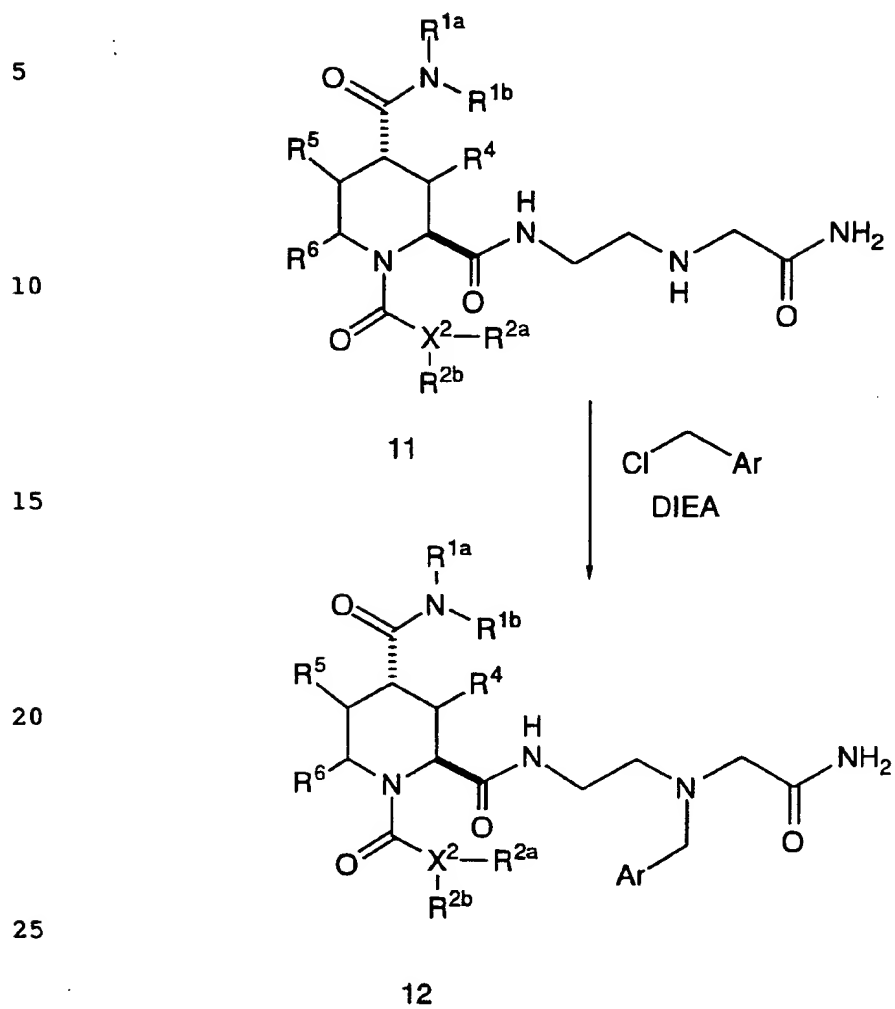
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SCHEME 5

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SCHEME 6

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SCHEME 6 (Continued)

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The compounds of the present invention in which $X^2 = N$ can be prepared according to the procedure given in Scheme 1. Esterification of the commercially available cis-piperidine-2,4-dicarboxylic acid under acidic conditions yields the diester 1. Acylation on nitrogen with, for example, N,N-diphenylcarbonyl chloride ($R^{1a} = R^{1b} = Ph$) provides the urea 2. Exposure of the diester 2 to one equivalent of aqueous base followed by acidification produces a mixture of the 4-carboxylic acid 3 and the 2-carboxylic acid 4, along with lesser quantities of the diacid. During the base hydrolysis step, epimerization to the more stable trans 2,4-disubstituted piperidine takes place. The extent of epimerization is dependent in part on the composition of the solvent: the lower the concentration of water present, the greater the degree of epimerization. If product enriched in cis-isomer is desired, the hydrolysis can be run in water with a minimum of organic solvent present, and the reaction should be stopped before completion.

The products 3 and 4 can be separated and carried on separately as shown in Schemes 2 and 3. In each case, the free acid is converted to the corresponding amide under standard conditions, the remaining ester is hydrolysed, for example, to give 5, and the revealed acid is functionalized to provide the product 6.

The side chains of interest can be prepared by several routes. For example, the ethylenediamine derivatives can be synthesized according to Scheme 4 if R^{10} and R^{11} do not contain groups susceptible to reduction with lithium aluminum hydride. If the N-methyl amide is not desired, the primary amine 7 can be used directly in the coupling reaction with the piperidine substrates.

For preparation of the N-methylcarboxamide containing sidechains, the chemistry shown in Scheme 5 can be employed. Mono-protection with an acylating agent such as di-t-butyl carbonate followed by alkylation of the remaining basic nitrogen with iodoacetamide is followed by orthogonal protection, for example, by CBZ chloride, to give the doubly protected intermediate 8. This compound can then be selectively deprotected to yield the desired side chain 9.

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After coupling 9 to 5 with a suitable condensing agent, for example, EDAC in the presence of HOBt in methylene chloride with a base present such as DIEA to free 9 from its salt, the product 10 can be deprotected under hydrogenolytic conditions to give the tetra-amide 11.
5 Alternatively, if groups incompatible with reducing conditions are present, HBr in acetic acid can be employed to cleave the CBZ protecting group. The amine 11 can be optionally alkylated, for example with a benzyl chloride derivative, to provide the product 12.

10 The object compounds of Formula I obtained according to the reactions as explained above can be isolated and purified in a conventional manner, for example, extraction, precipitation, fractional crystallization, recrystallization, chromatography, and the like.

The compounds of the present invention are capable of forming salts with various inorganic and organic acids and bases and
15 such salts are also within the scope of this invention. Examples of such acid addition salts include acetate, adipate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, ethanesulfonate, fumarate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, methanesulfonate, lactate, maleate,
20 methanesulfonate, 2-naphthalenesulfonate, oxalate, pamoate, persulfate, picrate, pivalate, propionate, succinate, tartrate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium, lithium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as
25 dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as: lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; diamyl sulfates;
30 long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; aralkyl halides like benzyl bromide and others. The non-toxic physiologically acceptable salts are preferred, although other salts are also useful, such as in isolating or purifying the product.

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The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze
5 drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

Although the reaction schemes described herein are reasonably general, it will be understood by those skilled in the art of organic synthesis that one or more functional groups present in a given
10 compound of Formula I may render the molecule incompatible with a particular synthetic sequence. In such a case an alternative route, an altered order of steps, or a strategy of protection and deprotection may be employed. In all cases the particular reaction conditions, including
15 reagents, solvent, temperature, and time, should be chosen so that they are consistent with the nature of the functionality present in the molecule.

The following examples are given for the purpose of illustrating the present invention and shall not be construed as being limitations on the scope or spirit of the invention.

20

EXAMPLE 1

Trans 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(3-(diethylamino)-propyl-aminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine

25

Step A: Cis dimethyl piperidine-2-(RS),4-(SR)-dicarboxylate

To a suspension of 0.36 g (2.08 mmole) of cis piperidine-2-(RS),4-(SR)-dicarboxylate in 20 mL of dry methanol was added 0.4 g (4.2 mmole) of concentrated sulfuric acid, and the mixture was heated at reflux under a drying tube for 72 hr. The cooled solution was treated
30 with solid sodium carbonate and water and was stirred for 2 hr, after which the bulk of the volatiles were removed *in vacuo*. The residue was purified by flash chromatography on 34 g of silica eluting with 700 mL of 2:100:0.1 methanol:methylene chloride: concentrated aqueous ammonia to give 342 mg (82%) of an oil.

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NMR (CDCl₃, 400 MHz, ppm): δ 1.45-1.60 (m, 2H), 1.83 (br s, 1H), 1.88 (dm, 1H), 2.27 (dm, 1H), 2.42 (dt, 1H), 2.63 (td, 1H), 3.20 (dm, 1H), 3.31 (dd, 1H), 3.66 (s, 3H), 3.70 (s, 3H).

5 Step B: Cis dimethyl 1-(N,N-diphenylaminocarbonyl)piperidine-2-(RS),4-(SR)-dicarboxylate

 A solution of 0.34 g (1.69 mmole) of cis dimethyl
piperidine-2-(RS),4-(SR)-dicarboxylate (from Example 1, Step A above),
0.431 g (1.86 mmole) of diphenylcarbonyl chloride, and 0.234 mL (1.86
10 mmole) of triethylamine in 6 mL of methylene chloride was stirred under
nitrogen at room temperature for 48 hr and then at reflux for 60 hr. After
cooling to room temperature, the mixture was purified by flash
chromatography on 65 g of silica eluting with 1.5 L of 66:33
hexanes:ethyl acetate to provide 567 mg (85%) of an oily solid.
15 NMR (CDCl₃, 400 MHz, ppm): δ 1.45-1.65 (m, 2H), 2.0-2.1 (m, 1H),
2.18-2.27 (m, 1H), 2.53 (pentet, 1H), 3.25-3.35 (m, 1H), 3.4-3.5 (m, 1H),
3.62 (s, 3H), 3.72 (s, 3H), 4.39 (t, 1H), 7.18-7.25 (m, 6H), 7.25-7.33 (m,
4H).

20 Step C: Trans methyl 1-(N,N-diphenylaminocarbonyl)piperidine-2-(RS)-carboxylic acid-4-(RS)-carboxylate and trans methyl 1-(N,N-diphenylaminocarbonyl)piperidine-4-(RS)-carboxylic acid-2-(RS)-carboxylate

 A solution of 63 mg (0.16 mmole) of cis dimethyl 1-(N,N-
25 diphenylaminocarbonyl)piperidine-2-(RS),4-(SR)-dicarboxylate (from
Example 1, Step B above) in 1 mL of methanol was treated with a
solution of 10 mg (0.16 mmole) of potassium hydroxide in 0.5 mL of
methanol at -10°C. The mixture was allowed to warm to room
temperature and was stirred for 18 hr, at which time 1 drop of water was
30 added. After stirring an additional 24 hr, 2 more drops of water were
added. After an additional 48 hr, the mixture was treated with 2 drops of
2 N aqueous hydrochloric acid and the volatiles were removed with a
stream of nitrogen. The residue was purified by flash chromatography on
16 g silica eluting with 500 mL of 1.8:100:0.12 methanol:methylene

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chloride:acetic acid to give 34 mg of high Rf product (A) and 20 mg of low Rf product (B) (total yield 88%). By analysis of mass spectral fragmentation patterns and NMR data for reaction products, A was assigned as trans methyl 1-(N,N-diphenyl-aminocarbonyl)piperidine-4-(RS)-carboxylic acid-2-(RS)-carboxylate and B was assigned as trans methyl 1-(N,N-diphenylaminocarbonyl)-piperidine-2-(RS)-carboxylic acid-4-(RS)-carboxylate.

Mass Spectrum (FAB): For Compound A - m/Z 383 (M+H, 100%), 337 (M-CO₂, 3%), 323 (M-CO₂Me, 13%), 196 (100%), 186 (70%), 168 (35%), 154 (25%), 136 (18%);

For Compound B - m/Z 383 (M+H, 100%), 337 (M-CO₂, 20%), 323 (M-CO₂Me, negligible), 196 (90%), 154 (85%), 136 (80%), 123 (25%).

NMR (CDCl₃, 400 MHz, ppm): For Compound A: δ 1.33 (qd, 1H; H_{5ax}), 1.5-1.7 (br m, 1H; H_{3ax}), 1.78 (d, 1H; H_{5eq}), 2.3-2.4 (m, 2H; H_{3eq}, H_{4ax}), 2.93 (td, 1H; H_{6ax}), 3.75 (s, 3H; CH₃), 3.88 (d, 1H; H_{6eq}), 4.99 (d, 1H; H_{2eq}), 7.05-7.15 (m, 6H; aromatic), 7.25-7.33 (m, 4H; aromatic).

For Compound B: δ 1.03 (qd, J = 13, 4, 1H; H_{5ax}), 1.57-1.69 (m, 2H; H_{3ax}, H_{5eq}), 2.41 (d, J = 12.2, 1H; H_{3eq}), 2.63 (tt, J = 12.4, 3.7, 1H; H_{4ax}), 2.93 (td, J = 13.3, 2.2, 1H; H_{6ax}), 3.63 (s, 3H; CH₃), 3.71 (br d, J = 12.4, 1H; H_{6eq}), 4.83 (d, J = 4.8, 1H; H_{2eq}), 7.05-7.35 (m, 10H, aromatic).

Step D: Trans methyl 1-(N,N-diphenylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine-2-(RS)-carboxylate

A solution of 0.034 g (0.089 mmole) of trans methyl 1-(N,N-diphenylaminocarbonyl)piperidine-4-(RS)-carboxylic acid-2-(RS)-carboxylate (from Example 1, Step C above) and 0.013 mg (0.098 mmole) of HOBT at 0°C under nitrogen was treated with 0.024 g (0.12 mmole) of EDAC. The bath was removed after 2 min, and after 35 min more, 0.028 g (0.18 mmole) of di-n-pentylamine was added, and the mixture was stirred for 20 hr. The reaction mixture was purified by flash chromatography on 16 g of silica eluting with 500 mL of 75:25 hexanes:

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ethyl acetate and then 200 mL of 50:50 hexanes:ethyl acetate to give 22 mg (48%) of an oil; a small amount of the cis isomer was also isolated. Mass Spectrum (FAB): m/z 523 (M+H, 15%), 463 (M-CO₂Me+H, 25%), 325 (M-Ph₂NCO, 100%), 196 (Ph₂NCO, 65%), 168, Ph₂N, 38%), 140 (60%).

NMR (CDCl₃, 400 MHz, ppm): δ 0.88 (q, 6H), 1.15-1.35 (m, 8H), 1.35-1.75 (m, 6H), 2.09 (d, 1H), 2.49 (tt, 1H), 2.86 (td, 1H), 3.1-3.3 (m, 4H), 3.76 (s, 3H), 3.90 (d, 1H), 4.99 (br s, 1H), 7.05-7.15 (m, 6H), 7.27-7.33 (m, 4H).

Step E: Trans 1-(N,N-diphenylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine-2-(RS)-carboxylic acid

To a suspension of 0.022 g (0.042 mmole) of trans methyl 1-(N,N-diphenylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine-2-(RS)-carboxylate (from Example 1, Step D above) in 0.75 mL of THF and 0.50 mL (0.042 mmole) of water was added 0.017 mL of 2.5 N aqueous sodium hydroxide, and the mixture was stirred at room temperature for 50 hr, at which time 0.005 mL (0.0014 mmole) more 2.5 N aqueous sodium hydroxide solution was added. After an additional 24 hr, the mixture was treated with 1 drop of 2 N aqueous hydrochloric acid and the volatiles were removed in a stream of nitrogen. The residue was purified by flash chromatography on 16 g of silica eluting with 400 mL of 3:100:0.1 methanol:methylene chloride:acetic acid to give 21 mg (100%) of an oil.

Mass Spectrum (FAB): m/z 508 (M+H, 40%), 462 (M-CO₂H, 15%), 343 (15%), 266 (40%), 196 (100%).
NMR (CDCl₃, 400 MHz, ppm): δ 0.86 (2 ot, 6H), 1.15-1.35 (m, 10H), 1.45 (pentet, 3H), 1.4-1.5 (m, 1H), 1.73 (td, 1H), 2.15 (br d, 1H), 2.88 (td, 2H), 3.08-3.20 (2H), 3.3-3.5 (m, 2H), 3.72 (br d, 1H), 4.78 (d, 1H), 7.10 (d, 4H), 7.17 (t, 2H), 7.34 (t, 4H).

Step F: Trans 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(3-(diethylamino)propylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine

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A solution of 0.022 g (0.043 mmole) of trans 1-(N,N-diphenylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)-piperidine-2-(RS)-carboxylic acid (from Example 1, Step E above) and 0.007 g (0.052 mmole) of HOBt in 1 mL of dry methylene chloride was cooled to 0°C under nitrogen and was treated with 0.013 g (0.052 mmole) of EDAC. The cooling bath was removed and after 55 min total the mixture was treated with 0.012 mL (0.087 mmole) of N,N-diethylethylenediamine, and the mixture was stirred at room temp for 22 hr. The mixture was purified by flash chromatography on 16 g of silica eluting with 7:100:0.2 methanol:methylene chloride:concentrated aqueous ammonia to give 28 mg (~100%) of an oil.

Mass Spectrum (FAB): m/Z 620 (M+H, 100%), 463 (M-CONH-(CH₂)₃NEt₂, 20%), 293 (15%), 196 (55%), 168 (25%), 112 (20%).

NMR (CDCl₃, 400 MHz, ppm): δ 0.85 (2 ot, 6H), 1.04 (t, 6H), 1.1-1.35 (m, 11H), 1.43 (pentet, 2H), 1.5-1.75 (m, 5H), 2.15 (br d, 1H), 2.4-2.7 (br m, 6H), 2.86 (td, 1H), 2.9-3.2 (m, 3H), 3.2-3.45 (m, 3H), 3.45-3.55 (m, 1H), 3.76 (br d, 1H), 4.76 (d, 1H), 7.07 (d, 4H), 7.15 (t, 2H), 7.33 (t, 4H).

EXAMPLE 2

Trans 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methylamino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine

Step A: Racemic cis and trans methyl 1-(N,N-diphenylaminocarbonyl)piperidine-2-carboxylic acid-4-carboxylate and racemic cis and trans methyl 1-(N,N-diphenylaminocarbonyl)piperidine-4-carboxylic acid-2-carboxylate

A solution of 0.478 g (1.21 mmole) of cis dimethyl 1-(N,N-diphenylaminocarbonyl)piperidine-2-(RS),4-(SR)-dicarboxylate (from Example 1, Step B above) in 6 mL of methanol was treated with 0.08 g (1.21 mmole) of potassium hydroxide in 2 mL of a 1:1 mixture of methanol:water at room temperature, and the mixture was stirred for 22 hr. The solution was then treated with 2 N aqueous hydrochloric acid

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until the pH was 4, and the mixture was concentrated *in vacuo*. The residue was purified by flash chromatography on 130 g of silica eluting with 3 L of 2.2:100:0.13 methanol:methylene chloride:concentrated aqueous ammonia to give 322 mg of high R_f material, which by proton NMR analysis was a 2:1 mixture of cis:trans methyl 1-(N,N-diphenylaminocarbonyl)piperidine-4-carboxylic acid-2-carboxylate and 62 mg of low R_f material, which by proton NMR was a 1:2.75 ratio of cis:trans methyl 1-(N,N-diphenylaminocarbonyl)piperidine-2-carboxylic acid-4-carboxylate (total yield 83%). Separation of cis and trans isomers could be achieved after further derivatization.

Step B: Preparation of N-(2-Methoxybenzyl)-N-methylethylenediamine

15 a) N-(2-Methoxybenzyl)-N-(methyl)aminoacetonitrile

A mixture of 2.0 g (13.2 mmole) of N-methyl-2-methoxybenzylamine, 0.99 g (13.2 mmole) of chloroacetonitrile, and 2.80 g (26.5 mmole) of powdered sodium carbonate was stirred in 30 mL of acetone at room temperature for 4 days. The mixture was concentrated *in vacuo* and the residue purified by flash chromatography on 130 g of silica gel eluting with 83: 17 hexanes: ethyl acetate to give 2.2 g (87%) of an oil. ¹H NMR (CDCl₃, 400 MHz, ppm): δ 2.43 (s, 3H), 3.48 (s, 2H), 3.62 (s, 2H), 3.83 (s, 3H), 6.88 (d, 1H), 6.93 (t, 1H), 7.2-7.3 (m, 2H).

25 b) N-(2-Methoxybenzyl)-N-methylethylenediamine

To a stirred slurry of 0.56 g (15 mmole) of lithium aluminum hydride in 15 mL of diethyl ether under an atmosphere of nitrogen was added a solution of 2.2 g (11.6 mmole) of N-(2-methoxybenzyl)-N-(methyl)aminoacetonitrile in 20 mL of diethyl ether. The mixture was heated at reflux for 1 hour and then was allowed to cool to room temperature. The excess hydride was quenched cautiously with aqueous sodium hydroxide, and the resulting suspension was filtered through a pad of sodium sulfate, which was rinsed with additional diethyl

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ether. The filtrate was concentrated *in vacuo* to give 2.25 g (~100%) of a clear oil.

¹H NMR (CDCl₃, 200 MHz, ppm): δ 1.30 (br s, 2H), 2.20 (s, 3H), 2.46 (t, 2H), 2.80 (t, 2H), 3.49 (s, 2H), 3.79 (s, 3H), 6.8-6.95 (m, 2H), 7.15-7.35 (m, 2H).

Step C: Trans methyl 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methylamino)ethylamino-carbonyl)piperidine-4-(RS)-carboxylate

A solution of 0.060 g (0.16 mmole) of a 1:2.75 cis:trans racemic mixture of methyl 1-(N,N-diphenylaminocarbonyl)piperidine-2-carboxylic acid-4-carboxylate (from Example 2, Step A above) and 0.023 g (0.17 mmole) of HOBt in 2 mL of dry methylene chloride was cooled to 0°C under nitrogen and was treated with 0.042 g (0.22 mmole) of EDAC. The cooling bath was removed and after 40 min total 0.061 g (0.31 mmole) of N-(2-methoxybenzyl)-N-methylethyl-enediamine (from Example 2, Step B above) was added and the mixture was stirred at room temperature for 24 hr. The mixture was purified by flash chromatography on 16 g of silica eluting with 400 mL of 4:100 methanol:methylene chloride and then 300 mL of 6:100:0.25 methanol:methylene chloride:concentrated aqueous ammonia to give 56 mg (64% yield uncorrected for purity of the starting material) of the trans product as an oil.

Mass Spectrum (FAB): m/Z 560 (M+H, 60%), 365 (8%), 337 (M-side chain, 18%), 196 (Ph₂CO, 45%), 164 (MeOPhCH₂N(Me)CH₂, 45%), 121 (MeOPhCH₂, 100%).

NMR (CDCl₃, 400 MHz, ppm): δ 0.98 (qd, 1H), 1.5-1.6 (m, 3H), 2.25 (br s, 3H), 2.43 (dm, 1H), 2.53 (t, 1H), 2.77 (tt, 1H), 2.84 (td, 1H), 3.25-3.35 (m, 1H), 3.3-3.43 (m, 1H), 2.56 (d, 1H), 3.61 (s, 3H), 3.78 (s, 3H), 3.80 (br d, 1H), 4.79 (d, 1H), 6.84 (app t, 2H), 7.03 (d, 4H), 7.05-7.10 (m, 1H), 7.11 (t, 2H), 7.15-7.30 (m, 6H).

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Step D: Trans 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methylamino)ethylaminocarbonyl) piperidine-4-(RS)-carboxylic acid

5 A solution of 0.044 g (0.078 mmole) of trans methyl 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methylamino)ethylaminocarbonyl)piperidine-4-(RS)-carboxylate (from Example 2, Step C above) in 1 mL of THF was treated with 0.7 mL of water and then 0.032 mL of a 2.5 N aqueous solution of sodium
10 hydroxide. The mixture was stirred for 20 hr, treated with 1 drop of 2 N aqueous hydrochloric acid, and the volatiles were removed in a stream of nitrogen. The mixture was further concentrated under high vacuum and the residue was carried on immediately in Example 10.

15 **Step E:** Trans 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methylamino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine

To a solution of 0.043 g (0.079 mmole) of trans 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methylamino)ethylamino carbonyl) piperidine-4-(RS)-carboxylic acid (from
20 Example 2, Step D above) and 0.012 g (0.087 mmole) of HOBT in 2.5 mL of dry methylene chloride under nitrogen at 0°C was added 0.021 g (0.11 mmole) of EDAC. The bath was removed and the mixture was allowed to stir at room temperature for 35 min, at which point 0.032 mL (0.158 mmole) of di-n-pentylamine was added and the mixture was allowed to
25 stir for 12 hr. The volatiles were removed in a stream of nitrogen and the residue was purified by flash chromatography on 16 g of silica eluting with 400 mL of 4:100 methanol:methylene chloride, to give 49 mg (91%) of an oil.

30 Mass Spectrum (FAB): m/Z 684 (M+H, 65%), 196 (Ph₂CO, 35%), 164 (MeOPhCH₂N(Me)CH₂, 45%), 121 (MeOPhCH₂, 100%).

NMR (CDCl₃, 400 MHz, ppm): δ 0.86 (t, 6H), 1.1-1.35 (m, 10H), 1.38-1.65 (m, 6H), 2.19 (d, 1H), 2.26 (s, 3H), 2.53 (br t, 2H), 2.82 (td, 1H), 2.85-2.95 (m, 1H), 3.0-3.15 (m, 2H), 3.25-3.63 (m, 5H), 3.79 (s, 3H),

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3.81 (d, 1H), 4.81 (d, 1H), 6.80-6.88 (m, 2H), 7.03 (d, 4H), 7.08-7.35 (m, 9H).

EXAMPLE 3

Trans 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(2-(N-(aminocarbonylmethyl)amino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine

Step A: N-(t-Butoxycarbonyl)ethylenediamine

To a solution of 1.65 g (27.5 mmole) of ethylenediamine in 20 mL of CH₂Cl₂ was added a solution of 2.00 g (9.16 mmole) of di-*t*-butyl dicarbonate in 8 mL of CH₂Cl₂ dropwise over 20 min at room temperature. After 48 hours, the mixture was filtered and the filtrate concentrated *in vacuo* to give 1.4 g of an oil.

¹H NMR (CDCl₃, 200 MHz, ppm): δ 1.13 (br s, 2H), 1.42 (s, 9H), 2.77 (t, 2H), 3.15 (q, 2H), 4.85 (v br s, 1H).

Step B: N-(t-Butoxycarbonyl)-N'-(benzyloxycarbonyl)-N'-(aminocarbonylmethyl)ethylenediamine

To a solution of 1.25 g (7.8 mmole) of N-(t-Butoxycarbonyl)ethylenediamine in 10 mL of acetonitrile was added 1.36 mL (7.8 mole) of DIEA followed by 1.44 g (7.8 mmole) of iodoacetamide at room temperature. After 90 min most of the solvent was removed *in vacuo* and the residue was taken up in 12 mL of CH₂Cl₂ and was treated with 1.36 mL (7.8 mmole) of DIEA and then 1.1 mL (7.8 mmole) of benzyl chloroformate. The resulting solution was stirred at room temperature for 2 days, and was then concentrated partly *in vacuo*. The residue was treated with 100 mL of ethyl acetate and 20 mL of 1 M aqueous tartaric acid and the layers were separated. The organic layer was washed with 2x15 mL of water, the tartaric acid layer was extracted with 30 mL of ethyl acetate, this extract was washed with 2x 10 mL of water, and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash

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chromatography on 131 g of silica gel eluting with 2.5 L of 100: 4 CH₂Cl₂:methanol to provide 1.5 g (55%) of an oil.

Mass Spectrum (FAB): m/Z 352 (M+H, 5%), 296 (M-isobutylene =H, 8%), 252 (M-isobutylene - CO₂ + H, 100%).

5 ¹H NMR (CDCl₃, 400 MHz, ppm): δ 1.40 (s, 9H), 3.29 (br s, 2H), 3.45 (t, 2H), 3.9 (s, 2H), 5.12 (s, 2H), 5.1-5.3 (br d, 1H), 5.59 (br s, 1H), 6.1-6.35 (br m, 1H), 7.25-7.35 (br m, 5H).

10 Step C: N-(benzyloxycarbonyl)-N-(aminocarbonylmethyl)ethylenediamine trifluoroacetic acid salt

A mixture of 0.16 g (0.46 mmole) of N-(t-Butoxy-carbonyl)-N'-(benzyloxycarbonyl)-N'-(aminocarbonylmethyl) ethylene-diamine and 0.4 mL of anisole was treated at 0°C with 2 mL of ice cold trifluoroacetic acid under nitrogen. After 90 min at 0°C, the solution was concentrated
15 *in vacuo* employing a high vacuum pump and with the heating bath at 48°C for several hours. The resulting oil was employed directly in Step D below.

20 Step D: Trans 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(2-(N-(benzyloxycarbonyl)-N-(aminocarbonylmethyl)amino)-ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine

A solution of 0.076 g (0.15 mmole) of trans 1-(N,N-diphenylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)-
25 piperidine-2-(RS)-carboxylic acid (from Example 1, Step E above) and 0.022 g (0.165 mmole) of HOBT in 6 mL of dry methylene chloride at 0°C under nitrogen was treated with 0.04 g (0.21 mmole) of EDAC. The cooling bath was removed and after 40 min a mixture of 0.11 g (0.3
30 mmole) of N-(benzyloxycarbonyl)-N-(aminocarbonylmethyl)-ethylenediamine trifluoroacetic acid salt (from Example 3, Step C above) and 0.042 mL (0.3 mmole) of triethylamine in 2 mL of methylene chloride was added, and the resulting solution was stirred for 19 hr at room temperature. The mixture was then concentrated *in vacuo* and the residue partitioned between 20 mL of water and 30 mL of ethyl acetate.

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The layers were separated and the aqueous layer was extracted with 25 mL of ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on 36 g of silica eluting with 1 L of 3:100 methanol:methylene chloride then 250 mL of 4:100 methanol:methylene chloride to give 56 mg (50%) of an oil.

Mass Spectrum (FAB): m/z 764 (M+Na, 1%), 742 (M+H, 1%), 726 (M-NH₂+H, 1%), 491 (55%), 462 (35%), 196 (Ph₂NCO, 100%), 168 (Ph₂N, 50%).

NMR (CDCl₃, 400 MHz, ppm): δ 0.87 (t, 6H), 1.05-1.35 (m, 10H), 1.4-1.65 (m, 6H), 2.0-2.2 (br s, 1H), 2.78-2.95 (m, 2H), 3.0-3.15 (m, 2H), 3.25-3.6 (m, 6H), 3.70 (br d, 1H), 3.90 (br s, 2H), 4.55-4.8 (br m, 1H), 5.0-5.2 (br s, 2H), 5.3-5.7 (br m, 1H), 6.1-6.3 (br m, 1H), 7.0-7.15 (br m, 3H), 7.13 (t, 2H), 7.25-7.4 (m, 9H), 7.59 (br s, 1H).

Step E: Trans 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(2-(N-(aminocarbonylmethyl)amino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine

A solution of 0.055 g (0.074 mmole) of trans 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(2-(N-(benzyloxycarbonyl)-N-(aminocarbonylmethyl)amino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine (prepared in Example 3, Step D above) in 5 mL of ethanol was treated with 32 mg of 10% palladium on carbon and the resulting slurry was then stirred under an atmosphere of hydrogen for 3 hr. The mixture was then filtered through a cake of Celite, the cake was washed with 100 mL of ethanol, and the filtrate was concentrated *in vacuo*, to give 39 mg (87%) of an oil.

Mass Spectrum (FAB): m/z 608 (M+H, 60%), 491 (95%), 463 (60%), 196 (Ph₂NCO, 100%), 168 (Ph₂N, 60%).

NMR (CDCl₃, 400 MHz, ppm): δ 0.88 (app q, 6H), 1.05-1.35 (m, 11H), 1.4-1.7 (m, 5H), 2.15 (d, 1H), 2.7-2.93 (m, 2H), 3.0-3.2 (m, 3H), 3.25-3.6 (m, 5H), 3.74 (d, 1H), 4.77 (d, 1H), 5.16 (br s, 1H), 7.04 (d, 4H), 7.05-7.15 (m, 1H), 7.17 (t, 2H), 7.3-7.4 (t, 4H), 7.89 (br t, 1H).

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EXAMPLE 4

Trans 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(2-(N-(2-methoxy-
benzyl)-(N-(aminocarbonylmethyl)amino)ethylaminocarbonyl)-4-(RS)-
5 (N,N-dipentylaminocarbonyl)piperidine

A solution of 0.027 g (0.044 mmole) of trans 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(2-(N-(aminocarbonylmethyl)amino)-ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine
10 (from Example 3, Step E above) and 0.011 mL (0.062 mmole) of DIEA in 1 mL of acetonitrile was treated with 0.014 mL (0.058 mmole) of a 50 wt % solution of 2-methoxybenzyl chloride in chloroform. The mixture was stirred at room temperature for 18 hr, then at 50°C for 11 hr and then at 70°C for 48 hr more. The mixture was cooled and concentrated *in vacuo*, and the residue was purified by flash chromatography on 16 g of
15 silica eluting with 3:100 methanol:methylene chloride to give 23 mg (72%) of an oil.

Mass Spectrum (FAB): m/Z 727 (M+H, 45%), 491 (35%), 462 (40%), 196 (Ph₂NCO, 60%), 168 (Ph₂N, 40%).

NMR (CDCl₃, 400 MHz, ppm): δ 0.85 (ot, 6H), 1.05-1.35 (m, 10H),
20 1.44 (pentet, J = 7.4, 3H), 1.5-1.65 (m, 3H), 2.10 (d, J = 13.4, 1H), 2.60 (t, J = 5.6, 2H), 2.81 (td, J = 12.9, 2.3, 1H), 3.0-3.3 (m, 6H), 3.35-3.6 (m, 3H), 3.68 (app d, J = 3.3, 2H), 3.73 (d, J = 13.5, 1H), 3.76 (s, 3H), 4.64 (d, J = 4.8, 1H), 4.88 (d, J = 2.7, 1H), 6.84-6.9 (m, 2H), 7.04 (app d, J =
25 7.5, 4H), 7.15-7.25 (m, 4H), 7.33 (app t, J = 8.3, 5H), 7.70 (br t, 1H).

EXAMPLE 5

Cis 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methylamino)ethylaminocarbonyl)-4-(SR)-(N,N-dipentylamino-
30 carbonyl)piperidine

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Step A: Racemic cis and trans methyl 1-(N,N-diphenylamino-carbonyl)-4-(N,N-dipentylaminocarbonyl)piperidine-2-carboxylate

5 A solution of 0.375 g (0.72 mmole) of a 2:1 mixture of
cis:trans methyl 1-(N,N-diphenylaminocarbonyl)piperidine-4-carboxylic
acid-2-carboxylate (from Example 2, Step A) and 0.011 mL (0.072
mmole) of DBU in 6 mL of methylene chloride was stirred at room
temperature under nitrogen for 36 hr. The mixture was treated with an
10 additional 0.033 mL of DBU and was heated at reflux for 14 hr. The
solvent was removed in a stream of nitrogen and the residue was
dissolved in 7 mL of toluene, and the resulting mixture was heated at 6 hr
at 90°C, at 110°C for 14 hr and at 120°C for 24 hr. The mixture was
cooled to room temperature and was concentrated *in vacuo*, and the
15 residue was partly purified by flash chromatography on 68 g of silica
eluting with 1.5 L of 66:33 hexanes:ethyl acetate and then 700 mL of
4:100:0.15 methanol:methylene chloride:acetic acid, to give trans methyl
1-(N,N-diphenylaminocarbonyl)-4-(RS)-(N,N-dipentylamino-
carbonyl)piperidine-2-(RS)-carboxylate as the major component and cis
20 methyl 1-(N,N-diphenylaminocarbonyl)-4-(RS)-(N,N-dipentylamino-
carbonyl)piperidine-2-(SR)-carboxylate as the minor component. Final
purification of the latter material was carried out by flash chromato-
graphy on 36 g of silica eluting with 1.1 L 75:25 hexanes:ethyl acetate to
give 25 mg of cis methyl 1-(N,N-diphenyl-aminocarbonyl)-4-(RS)-(N,N-
25 dipentylaminocarbonyl)piperidine-2-(SR)-carboxylate.
NMR (CDCl₃, 400 MHz, ppm): δ 0.86 (t, 3H), 0.89 (t, 3H), 1.15-1.35
(m, 8H), 1.38-1.65 (m, 6H), 1.95 (dt, 1H), 2.03-2.13 (ot, 1H), 2.5-2.6 (m,
1H), 3.1-3.25 (m, 5H), 3.48-3.55 (m, 1H), 3.72 (s, 3H), 4.22 (dd, 1H),
7.09-7.16 (m, 5H), 7.25-7.30 (m, 5H).

30 **Step B:** Cis 1-(N,N-diphenylaminocarbonyl)-4-(RS)-(N,N-dipentyl-aminocarbonyl)piperidine-2-(SR)-carboxylic acid

 A solution of 0.025 g (0.048 mmole) of cis methyl 1-(N,N-
diphenylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)-
piperidine-2-(SR)-carboxylate in 1 mL of THF and 0.7 mL of water was

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5 treated with 0.019 mL of aqueous 10% sodium hydroxide, and the mixture was stirred at room temperature for 24 hr. The solution was treated with 1 drop of 2 N aqueous hydrochloric acid and the volatiles were removed with a vigorous stream of nitrogen. The residual white solid was carried on in Step C below.

Step C: Cis 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methylamino)ethylaminocarbonyl)-4-(SR)-(N,N-dipentylaminocarbonyl)piperidine

10 A solution of 0.024 g (0.047 mmole) of crude cis 1-(N,N-diphenylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)-piperidine-2-(SR)-carboxylic acid (from Example 5, Step B) and 0.007 g (0.052 mmole) of HOBt in 1 mL of dry methylene chloride was cooled to 0°C under an atmosphere of nitrogen and the mixture was treated with
15 0.013 g (0.066 mmole) of EDAC. The cooling bath was removed and after 30 min 0.018 g (0.095 mmole) of N-(2-Methoxy-benzyl)-N-methylethylenediamine (from Example 2, Step B) in 1 mL of methylene chloride was added, and the mixture was stirred at room temperature for
20 20 hr. The reaction mixture was then purified by flash chromatography on 16 g of silica eluting with 450 mL of 4:100:0.1 methanol:methylene chloride:concentrated aqueous ammonia then 5:100:0.1 methanol:methylene chloride:concentrated aqueous ammonia to give 25 mg (78%) of an oil.

25 Mass Spectrum (FAB): m/Z 684 (M+H, 80%), 462 (25%), 196 (Ph₂NCO, 60%), 168 (Ph₂N, 30%), 121 (MeOPhCH₂, 100%).

NMR (CDCl₃, 400 MHz, ppm): δ 0.84 (t, 3H), 0.92 (t, 3H), 1.15-1.6 (m, 14H), 1.87 (dt, 1H), 2.1-2.25 (m, 5H), 2.53 (br s, 3H), 3.06-3.65 (m, 9H), 3.79 (s, 3H), 4.10 (dd, 1H), 6.50 (br s, 1H), 6.84-7.0 (m, 2H), 7.05-7.15 (m, 6H), 7.18-7.26 (m, 6H).

EXAMPLE 6

Trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine-2-(RS)-carboxylic acid

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Step A: N-(3-chlorophenyl)-N-phenylcarbamoyl chloride

A solution of 20.4 g (100 mmole) of commercial 3 chloro-diphenylamine in 40 mL of toluene and 100 mL of 1.93 M phosgene in toluene were combined and heated at 90°C under nitrogen for 2 hrs with stirring. The red-orange solution was cooled, flushed with nitrogen for 2 hrs to remove excess phosgene and concentrated *in vacuo* to provide 15.4 g (58%) of a red-orange oil which was homogeneous by TLC (4:1 hexanes: ethyl acetate, R_f = 0.8).

Mass Spectrum (FAB): m/Z 266 (M+H).

IR (neat): 1740 cm⁻¹, no NH absorption.

Step B: Cis dimethyl 1-(N-(3-chlorophenyl)-N-(phenyl)amino-carbonyl)piperidine-2-(RS),4-(SR)-dicarboxylate

A solution of 0.159 g (0.79 mmole) of cis dimethyl piperidine-2-(RS),4-(SR)-dicarboxylate (from Example 1, Step A above) and 0.263 g (1 mmole) of N-(3-chlorophenyl)-N-phenyl-carbamoyl chloride in 3 mL of dry methylene chloride was treated with 0.131 mL (0.95 mmole) of triethylamine, and the mixture was stirred at room temperature for 24 hr and at reflux for 86 hr. The mixture was purified by flash chromatography on 36 g of silica eluting with 1 L of 75:25 hexanes:ethyl acetate to give 335 mg (98%) of an oil.

NMR (CDCl₃, 400 MHz, ppm): δ 1.5-1.7 (dm, 2H), 2.0-2.1 (m, 1H), 2.13-2.2 (m, 1H), 2.54 (pentet, 1H), 3.28-3.38 (m, 1H), 3.41 (dd, 1H), 3.63 (s, 3H), 3.72 (s, 3H), 4.44 (t, 1H), 6.98 (dd, 1H), 7.05-7.25 (m, 6H), 7.33 (app t, 2H).

Step C: Trans methyl 1-(N-(3-chlorophenyl)-N-(phenyl)amino-carbonyl)piperidine-2-(RS)-carboxylic acid-4-(RS)-carboxylate and trans methyl 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)piperidine-4-(RS)-carboxylic acid-2-(RS)-carboxylate

A solution of 0.325 g (0.75 mmole) of cis dimethyl 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)piperidine-2-(RS),4-(SR)-dicarboxylate in 6 mL of methanol was treated with a solution of 0.050 g

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(0.75 mmole) of 85% potassium hydroxide in 2 mL of methanol, and the resulting mixture was stirred at room temperature for 68 hr at which point 4 drops of water was added and the mixture was stirred for an additional 96 hr. The reaction was then treated with 2 N aqueous hydrochloric acid until the pH was 3.5 and the mixture was concentrated *in vacuo*. The residue was purified by flash chromatography on 130 g of silica eluting with 3 L of 2:100:0.2 methanol:methylene chloride:acetic acid to give 143 mg (45%) of higher Rf material (trans methyl 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)piperidine-4-(RS)-carboxylic acid-2-(RS)-carboxylate) and 114 mg (36%) of lower Rf material (trans methyl 1-(N-(3-chlorophenyl)-N-(phenyl)amino-carbonyl)piperidine-2-(RS)-carboxylic acid-4-(RS)-carboxylate). Proton NMR evaluation revealed that the higher Rf compound was a 9:1 trans:cis mixture. NMR (CDCl₃, 400 MHz, ppm): δ for higher Rf component: 1.35 (qd, 1H), 1.6-1.7 (m, 1H), 1.81 (br d, 1H), 2.35-2.45 (m, 2H), 2.92 (td, 1H), 3.77 (s, 3H), 3.86 (br d, 1H), 5.00 (br s, 1H), 6.93 (dd, 1H), 7.0-7.25 (m, 6H), 7.33 (app t, 2H); for lower Rf component: 1.20 (qd, 1H), 1.64 (td, 1H), 1.71 (br d, 1H), 2.42 (br d, 1H), 2.51 (tt, 1H), 3.96 (td, 1H), 3.64 (s, 3H), 3.78 (br d, 1H), 4.92 (br d, 1H), 6.96 (dd, 1H), 7.03-7.23 (m, 6H), 7.33 (app t, 2H).

Step D: Trans methyl 1-(N-(3-chlorophenyl)-N-(phenyl)amino-carbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine-2-(RS)-carboxylate

A solution of 0.140 g (0.34 mmole) of trans methyl 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)piperidine-4-(RS)-carboxylic acid-2-(RS)-carboxylate and 0.050 g (0.37 mmole) of HOBt in 5 mL of dry methylene chloride was cooled to 0°C under nitrogen and was treated with 0.090 g (0.047 mmole) of EDAC. The cooling bath was removed and after 40 min 0.135 mL (0.67 mmole) of di-n-pentylamine was added, and the mixture was stirred at room temperature for 24 hr. The mixture was concentrated *in vacuo* and the residue partly purified by flash chromatography on 35 g of silica eluting with 900 mL of 1:100 methanol:methylene chloride. Final purification was carried out by flash

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chromatography on 68 g of silica eluting with 2 L of 80:20 hexanes:ethyl acetate and then 600 mL of 67:33 hexanes:ethyl acetate to give 144 mg (77%) of a clear oil.

5 Mass Spectrum (FAB): m/z 557 (M+H, 20%), 325 (M-CIPhN(Ph)CO, 100%), 230 (CIPhN(Ph)CO, 25%), 140 (50%).

NMR (CDCl₃, 400 MHz, ppm): δ 0.8-0.9 (ot, 6H), 1.15-1.35 (m, 9H), 1.4-1.8 (m, 6H), 2.13 (br d, 1H), 2.50 (tt, 1H), 2.84 (td, 1H), 3.1-3.35 (m, 4H), 3.78 (s, 3H), 3.86 (br d, 1H), 5.03 (br s, 1H), 6.94 (dd, 1H), 7.0-7.25 (m, 6H), 7.33 (app t, 2H).

10

Step E: Trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine-2-(RS)-carboxylic acid

15

A solution of 0.144 g (0.26 mmole) of trans methyl 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine-2-(RS)-carboxylate in 3 mL of THF was treated with 2.5 mL of water and then 0.104 mL of a 2.5 N aqueous solution of sodium hydroxide, and the mixture was stirred at room temperature for 14 hr. The reaction mixture was treated with 2 N aqueous hydrochloric acid, 6 mL water and methylene chloride/ethyl acetate, the layers were separated, and the aqueous layer was extracted with 2x20 mL of ethyl acetate. The organic extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on 36 g of silica eluting with 1 L of 2.5:100:0.1 methanol:methylene chloride:acetic acid, to give 130 mg (93%) of a viscous oil.

20

25

Mass Spectrum (FAB): m/z 543 (M+H, 35%), 267 (100%), 230 (CIPhN(Ph)CO, 55%), 204 (55%), 158 (50%).

30

NMR (CDCl₃, 400 MHz, ppm): δ 0.8-0.9 (m, 6H), 1.15-1.35 (m, 9H), 1.45 (pentet, 4H), 1.5-1.6 (m, 1H), 1.74 (td, 1H), 2.17 (d, 1H), 2.8-2.95 (2H), 3.1-3.2 (m, 2H), 3.3-3.45 (m, 2H), 3.72 (d, 1H), 4.83 (d, 1H), 6.99 (dd, 1H), 7.05 (m, 1H), 7.09-7.17 (m, 3H), 7.2-7.3 (m, 2H), 7.38 (app t, 2H).

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EXAMPLE 7

5 Trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methylamino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine

10 Step A: Trans methyl 1-(N-(3-chlorophenyl)-N-(phenyl)amino-carbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methyl-amino)ethylaminocarbonyl)piperidine-4-(RS)-carboxylate

15 A suspension of 0.112 g (0.27 mmole) of trans methyl 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)piperidine-2-(RS)-carboxylic acid-4-(RS)-carboxylate (from Example 6, Step C) in 6 mL of methylene chloride was treated with 1 mL of acetonitrile and 0.040 g (0.29 mmole) of HOBt. The mixture was cooled to 0°C and was treated with 0.072 g
20 (0.38 mmole) of EDAC. The cooling bath was removed, the mixture was stirred for an additional 35 min and then 0.104 g (0.54 mmole) of N-(2-methoxybenzyl)-N-methylethyl-enediamine (from Example 2, Step B) was added and the reaction was stirred for 16 hr. The solution was partly concentrated and the residue was purified by flash chromatography on 16
25 g of silica eluting with 300 mL of 3.5:100 methanol:methylene chloride then 200 mL of 5:100 methanol:methylene chloride to give 108 mg (68%) of an oil.

30 Mass Spectrum (FAB): m/Z 593 (M+H, 100%), 164 (20%), 122 (MeOPhCH₂+H, 50%).
25 NMR (CDCl₃, 400 MHz, ppm): δ 0.99 (qd, 1H), 1.5-1.6 (m, 2H), 2.25 (br s, 3H), (2.41 (dd, 1H), 1.5-1.6 (m, 2H), 2.76 (tt, 1H), 2.88 (td, 1H), 3.25-3.35 (m, 1H), 3.4-3.5 (m, 1H), 3.5-3.6 (m, 2H), 3.61 (s, 3H), 3.77 (br d, 1H), 3.79 (s, 3H), 4.78 (d, 1H), 6.8-6.95 (m, 3H), 6.95-7.22 (m, 7H), 7.25-7.35 (m, 3H).

Step B: Trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methylamino)ethyl-aminocarbonyl)piperidine-4-(RS)-carboxylic acid

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A solution of 0.108 g (0.18 mmole) of trans methyl 1-(N-(3-chlorophenyl)-N-(phenyl)-aminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methylamino)ethylaminocarbonyl)piperidine-4-(RS)-carboxylate in 2.2 mL of dry THF was treated with 1.5 mL of water and then 0.073 mL of a 2.5 N aqueous solution of sodium hydroxide, and the mixture was stirred at room temperature for 15 hr. The mixture was concentrated partly in a vigorous stream of nitrogen and partly *in vacuo*, and was used as is in further reactions.

Step C: Trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methylamino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)-piperidine

According to the procedure given in Example 2, Step E, 0.051 g of trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methylamino)ethylaminocarbonyl)-piperidine-4-(RS)-carboxylic acid gave 43 mg (68%) of an oil. Mass Spectrum (FAB): m/z 719 (M+H, 45%), 230 (C₁PhN(CO)Ph, 20%), 164 (MeOPhCH₂N(Me)CH₂, 35%), 121 (MeOPhCH₂, 100%). NMR (CDCl₃, 400 MHz, ppm): δ 0.86 (t, 6H), 1.15-1.65 (m, 16H), 2.17 (d, 1H), 2.27 (br s, 3H), 2.5-2.6 (m, 2H), 2.7-2.95 (m, 2H), 3.0-3.15 (m, 2H), 3.25-3.7 (m, 5H), 3.78 (br d, 1H), 3.79 (s, 3H), 4.81 (d, 1H), 6.8-6.96 (m, 3H), 7-7.35 (m, 10H).

EXAMPLE 8

Trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methylamino)ethylaminocarbonyl)-4-(RS)-(N,N-dibenzylaminocarbonyl)piperidine

According to the procedure given in Example 2, Step E, 0.051 g of trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methylamino)ethylaminocarbonyl)-piperidine-4-(RS)-carboxylic acid and 0.035 g of dibenzylamine gave 22 mg (33%) of an oil.

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Mass Spectrum (FAB): m/z 759 (M+H, 10%), 230 (CIPhN(CO)Ph, 10%), 164 (MeOPhCH₂N(Me)CH₂, 30%), 121 (MeOPhCH₂, 100%).
NMR (CDCl₃, 400 MHz, ppm): δ 1.37 (qd, 1H), 1.69 (td, 2H), 2.11 (br s, 3H), 2.33 (br d, 1H), 2.48 (br t, 2H), 2.75 (td, 1H), 3.05 (tt, 1H), 3.2-3.3 (m, 1H), 3.35-3.45 (m, 1H), 3.47-3.60 (m, 2H), 3.74 (br d, 1H), 3.76 (s, 3H), 4.07 (d, 1H), 4.33 (d, 1H), 4.82 (d, 1H), 4.83 (br d, 1H), 4.97 (d, 1H), 6.78-6.85 (m, 2H), 6.92 (d, 1H), 7.05-7.35 (m, 20H).

EXAMPLE 9

Trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-2-(RS)-(2-(N-(benzyloxycarbonyl)-N-(aminocarbonylmethyl)amino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine

According to the procedure given in Example 3, Step D, 0.11 g of trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine-2-(RS)-carboxylic acid (from Example 6, Step E above) gave 69 mg (44%) of the product, along with 49 mg of recovered starting material.

Mass Spectrum (FAB): m/z 776 (M+H, 5%), 573 (30%), 525 (100%), 497 (45%), 293 (65%), 267 (75%), 230 (95%), 167 (55%), 158 (60%).
NMR (CDCl₃, 400 MHz, ppm): most signals broadened due to rotomers
 δ 0.83-0.93 (m, 6H), 1-1.7 (m, 18H), 2-2.2 (br m, 1H), 2.8-2.9 (m, 2H), 3.05-3.15 (m, 2H), 3.2-3.7 (m, 6H), 3.8-4.0 (m, 2H), 4.6-4.8 (m, 1H), 5-5.2 (m, 2H), 5.3-5.5 (m, 1H), 6.1-6.2 (br s, 1H), 6.94 (d, 1H), 7.05-7.15 (m, 3H), 7.15-7.4 (m, 10H), 7.5-7.65 (m, 1H).

EXAMPLE 10

Trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-2-(RS)-(2-N-(aminocarbonylmethyl)amino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine

A mixture of 0.069 g (0.089 mmole) of trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-2-(RS)-(2-(N-(benzyloxycarbonyl)-N-(aminocarbonylmethyl)amino)ethylaminocarbonyl)-4-

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(RS)-(N,N-dipentylaminocarbonyl)piperidine (from Example 9) and 5 mL of a 30% solution of HBr in acetic acid was stirred at room temperature for 1 hr under a drying tube. Nitrogen was bubbled through the mixture for 2 hr to remove HBr and the mixture was concentrated *in vacuo*. The residue was treated with methylene chloride, methanol and aqueous ammonia, and the mixture was purified by flash chromatography on 36 g of silica eluting with 1 L of 4:100 methanol: methylene chloride, then 500 mL of 5:100 methanol:methylene chloride to give 33 mg (58%) of an oil.

5

10 NMR (CDCl₃, 400 MHz, ppm): δ 0.8-0.9 (m, 6H), 1.15-1.35 (m, 8H), 1.4-1.7 (m, 8H), 2.17 (d, 1H), 2.7-2.9 (m, 3H), 3-3.6 (m, 8H), 3.72 (d, 1H), 4.74 (d, 1H), 5.03 (s, 1H), 6.9-7.5 (m, 9H), 7.81 (t, 1H).

EXAMPLE 11

15

Trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-(N-(aminocarbonylmethyl)amino)ethylamino-carbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine

According to the procedure in Example 4, 0.016 g (0.025 mmole) of trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-2-(RS)-(2-(N-(aminocarbonylmethyl)amino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine gave 15 mg (79%) of an oil.

Mass Spectrum (FAB): m/Z 762 (M+H, 16%), 525 (8%), 497 (8%), 293 (15%), 230 (17%), 121 (100%).

25 NMR (CDCl₃, 400 MHz, ppm): δ 0.8-0.9 (m, 6H), 1.1-1.35 (m, 10H), 1.4-1.65 (m, 8H), 2.09 (d, 1H), 2.60 (t, 2H), 2.8-2.9 (1H), 3-3.2 (m, 6H), 3.2-3.3 (m, 1H), 3.3-3.6 (m, 3H), 3.6-3.75 (m, 3H), 3.77 (s, 3H), 4.64 (d, 1H), 5.00 (d, 1H), 6.85-6.95 (m, 4H), 7.04 (app d, 1H), 7.1-7.3 (m, 5H), 7.3-7.4 (2H), 7.53 (br t, 1H).

30

EXAMPLE 12

Typical Pharmaceutical Compositions Containing a Compound of the Invention

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A: Dry Filled Capsules Containing 50 mg of Active Ingredient Per Capsule

	<u>Ingredient</u>	<u>Amount per capsule (mg)</u>
5	Active ingredient	50
	Lactose	149
	Magnesium stearate	<u>1</u>
	Capsule (size No. 1)	200

10 The active ingredient can be reduced to a No. 60 powder and the lactose and magnesium stearate can then be passed through a No. 60 blotting cloth onto the powder. The combined ingredients can then be mixed for about 10 minutes and filled into a No. 1 dry gelatin capsule.

15 B: Tablet

A typical tablet would contain the active ingredient (25 mg), pregelatinized starch USP (82 mg), microcrystalline cellulose (82 mg) and magnesium stearate (1 mg).

20 C: Suppository

Typical suppository formulations for rectal administration contain the active ingredient (0.08-1.0 mg), disodium calcium edetate (0.25-0.5 mg), and polyethylene glycol (775-1600 mg). Other
25 suppository formulations can be made by substituting, for example, butylated hydroxytoluene (0.04-0.08 mg) for the disodium calcium edetate and a hydrogenated vegetable oil (675-1400 mg) such as Suppocire L, Wecobee FS, Wecobee M, Witepsols, and the like, for the polyethylene glycol.

30 D: Injection

A typical injectible formulation contains the acting ingredient sodium phosphate dibasic anhydrous (11.4 mg), benzyl alcohol (0.01 ml) and water for injection (1.0 ml).

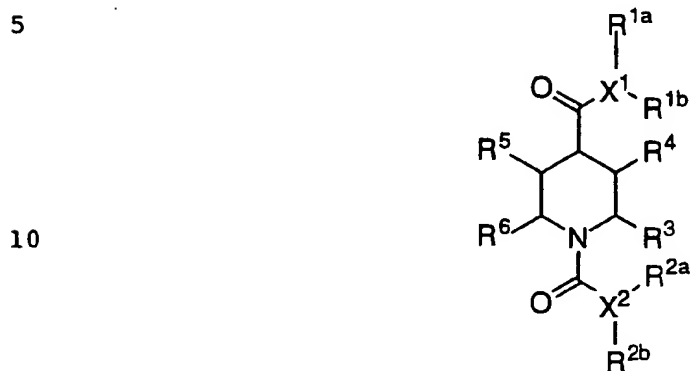
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While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

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WHAT IS CLAIMED IS:

1. A compound of structural formula:



I

or a pharmaceutically acceptable salt thereof, wherein:

R^{1a} is selected from the group consisting of:

- 20
- 1) H,
 - 2) C₁-8 alkyl,
 - 3) phenyl, either unsubstituted or substituted with one or two substituents selected from the group consisting of:
 - a) -C₁-4 alkyl,
 - b) -halo,
 - 25 c) -OH,
 - d) -CF₃,
 - e) -NH₂,
 - f) -NH(C₁-4 alkyl),
 - g) -N(C₁-4 alkyl)(C₁-4 alkyl),
 - 30 h) -CO₂H,
 - i) -CO₂(C₁-4 alkyl), and
 - j) -C₁-4 alkoxy;

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- 4) -C₁₋₄alkyl-phenyl, wherein the phenyl is either unsubstituted or substituted with one or two substituents selected from:

- 5 a) -C₁₋₄ alkyl,
 b) -halo,
 c) -OH,
 d) -CF₃,
 e) -NH₂,
10 f) -NH(C₁₋₄ alkyl),
 g) -N(C₁₋₄ alkyl)₂,
 h) -CO₂H,
 i) -CO₂(C₁₋₄ alkyl), and
 j) -C₁₋₄ alkoxy;

- 15 R1b is selected from the group consisting of:

- 1) R1a,
 2) -C₃₋₇ cycloalkyl, and
 3) -CH₂-R1a;

- 20 R2a and R2b are independently phenyl, either unsubstituted or substituted with one or two substituents selected from the group consisting of:

- 1) -C₁₋₄ alkoxy,
 2) -halo,
 3) -OH,
25 4) -CF₃,
 5) -NH₂,
 6) -NH(C₁₋₄ alkyl),
 7) -N(C₁₋₄ alkyl)₂,
 8) -CO₂H,
30 9) -CO₂(C₁₋₄ alkyl), and
 10) -C₁₋₆ alkyl, either unsubstituted or substituted with one or more substituents selected from the group consisting of:
 a) -halo,
 b) -OH,

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- 5
- c) -CF₃,
 - d) -NH₂,
 - e) -NH(C₁₋₄ alkyl),
 - f) -N(C₁₋₄ alkyl)(C₁₋₄ alkyl),
 - g) -CO₂H,
 - h) -CO₂(C₁₋₄ alkyl),
 - i) C₁₋₄alkoxy,
 - j) -S(O)_x(C₁₋₄ alkyl) wherein
x is 0, 1 or 2,
 - 10 k) -C₃₋₇ cycloalkyl;

and the phenyl groups of R^{2a} and R^{2b} may be joined together at the ortho carbon atoms through a carbon-carbon single bond or C₁₋₃ alkylene to form a tricyclic group with the X² to which they are attached;

15 X¹ is -N, -CH or O, and if X¹ is O, R^{1a} is absent;

X² is -N or -CH;

20 R³ is selected from the group consisting of:

- 1) -CONR⁷R⁸, and
- 2) -CO₂R⁹;

25 R⁴, R⁵ and R⁶ are H or are independently selected from the definitions of R³;

R⁷ is C₁₋₆ alkyl substituted with one or more substituents selected from the group consisting of :

- 30
- 1) -NHR¹⁰,
 - 2) -NR¹⁰R¹¹,
 - 3) -NHCO(C₁₋₆ alkyl),
 - 4) -NR¹⁰CO₂R¹¹,
 - 5) -N(R¹⁰)(C₁₋₆ alkyl)CONHR¹¹),
 - 6) -N(CO₂R¹⁰)(C₁₋₆ alkyl)CONHR¹¹), and
 - 7) -NR¹⁰(C₁₋₆ alkyl)CONHR¹¹;

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R⁸ is H, C₁₋₆ alkyl or is independently selected from the definitions of R⁷;

5 R⁹ is H or -CH₂-phenyl, wherein the phenyl is either unsubstituted or substituted with one or more substituents selected from the group consisting of:

- 1) -C₁₋₄ alkoxy,
- 10 2) -halo,
- 3) -OH,
- 4) -CF₃,
- 5) -NH₂,
- 6) -NH(C₁₋₄ alkyl),
- 7) -N(C₁₋₄ alkyl)₂,
- 15 8) -CO₂H,
- 9) -CO₂(C₁₋₄ alkyl), and
- 10) -C₁₋₆ alkyl, either unsubstituted or substituted with one or more substituents selected from the group consisting of:
 - 20 a) -halo,
 - b) -OH,
 - c) -CF₃,
 - d) -NH₂,
 - e) -NH(C₁₋₄ alkyl),
 - 25 f) -N(C₁₋₄ alkyl)(C₁₋₄ alkyl),
 - g) -CO₂H,
 - h) -CO₂(C₁₋₄ alkyl),
 - i) C₁₋₄alkoxy,
 - j) -S(O)_x(C₁₋₄ alkyl) wherein
30 x is 0, 1 or 2,
 - k) -C₃₋₇ cycloalkyl;

R¹⁰ is H, C₁₋₆ alkyl, or -(C₁₋₆ alkyl)-phenyl, wherein the phenyl is either unsubstituted or substituted with one or more substituents selected from the group consisting of:

- 1) -C₁₋₄ alkoxy,

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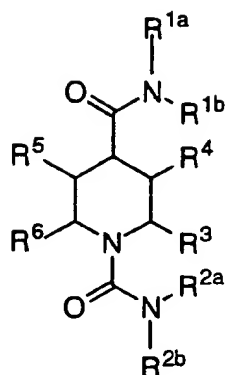
- 2) -halo,
3) -OH,
4) -CF₃,
5) -NH₂,
5 6) -NH(C₁₋₄ alkyl),
7) -N(C₁₋₄ alkyl)₂,
8) -CO₂H,
9) -CO₂(C₁₋₄ alkyl), and
10 10) -C₁₋₆ alkyl, either unsubstituted or substituted with one or
more substituents selected from the group consisting of:
a) -halo,
b) -OH,
c) -CF₃,
d) -NH₂,
15 e) -NH(C₁₋₄ alkyl),
f) -N(C₁₋₄ alkyl)(C₁₋₄ alkyl),
g) -CO₂H,
h) -CO₂(C₁₋₄ alkyl),
i) C₁₋₄alkoxy,
20 j) -S(O)_x(C₁₋₄ alkyl) wherein x is 0, 1 or 2,
k) -C₃₋₇ cycloalkyl; and

25 R¹¹ is H, C₁₋₆ alkyl, or is independently selected from the definitions of R¹⁰.

2. The compound of Claim 1 wherein X¹ and X² are both N of structural formula:

30

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or a pharmaceutically acceptable salt thereof.

3. The compound of Claim 2 wherein:

R^{1a} is selected from the group consisting of:

- 1) C₅-6 alkyl,
- 2) phenyl,
- 3) -CH₂-phenyl,

R^{1b} is selected from the definitions of R^{1a};

R^{2a} and R^{2b} are independently phenyl, either unsubstituted or substituted with one substituent selected from the group consisting of:

- 1) -OCH₃,
- 2) -Cl,
- 3) -CF₃,
- 4) -CH₃;

R³ is selected from the group consisting of:

- 1) -CONR⁷R⁸, and
- 2) -CO₂R⁹;

R⁷ is C₁-6 alkyl substituted with one or more substituents selected from the group consisting of:

- 1) -NHR¹⁰,

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- 5
- 2) -NR¹⁰R¹¹,
 - 3) -NHCO (C₁₋₆ alkyl),
 - 4) -NR¹⁰CO₂R¹¹,
 - 5) -N(CO₂R¹⁰)(C₁₋₆ alkyl)CONHR¹¹),
 - 6) -NR¹⁰(C₁₋₆ alkyl)CONHR¹¹;

R⁸ is H, C₁₋₆ alkyl or is independently selected from the definitions of R⁷;

- 10
- R⁹ is H or -CH₂-phenyl, wherein the phenyl is either unsubstituted or substituted with one or more substituents selected from the group consisting of:

- 15
- 1) -C₁₋₄ alkoxy,
 - 2) -halo,
 - 3) -OH,
 - 4) -CF₃,
 - 5) -NH₂,
 - 6) -NH(C₁₋₄ alkyl),
 - 7) -N(C₁₋₄ alkyl)₂,
 - 8) -CO₂H,
 - 9) -CO₂(C₁₋₄ alkyl), and
 - 10) -C₁₋₆ alkyl, either unsubstituted or substituted with one or more substituents selected from the group consisting of:
- 25
- a) -halo,
 - b) -OH,
 - c) -CF₃,
 - d) -NH₂,
 - e) -NH(C₁₋₄ alkyl),
 - f) -N(C₁₋₄ alkyl)(C₁₋₄ alkyl),
 - g) -CO₂H,
 - h) -CO₂(C₁₋₄ alkyl),
 - 30 i) C₁₋₄alkoxy,
 - j) -S(O)_x(C₁₋₄ alkyl) wherein
x is 0, 1 or 2,
 - k) -C₃₋₇ cycloalkyl;

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R¹⁰ is -(C₁₋₄ alkyl)-phenyl, wherein the phenyl is either unsubstituted or substituted with one or more substituents selected from the group consisting of:

- 5
- 1) -OCH₃,
 - 2) -Cl,
 - 3) -CF₃,
 - 4) -CH₃; and

10 R¹¹ is H, C₁₋₆ alkyl, or is independently selected from the definitions of R¹⁰.

4. The compound of Claim 2 wherein:

15 R^{1a} is selected from the group consisting of:

- 1) H,
- 2) C₁₋₈ alkyl,
- 3) phenyl, either unsubstituted or substituted with one or two substituents selected from the group consisting of:

20 a) -C₁₋₄ alkyl,

b) -halo,

c) -OH,

d) -CF₃,

e) -NH₂,

25 f) -NH(C₁₋₄ alkyl),

g) -N(C₁₋₄ alkyl)(C₁₋₄ alkyl),

h) -CO₂H,

i) -CO₂(C₁₋₄ alkyl), and

30 j) -C₁₋₄ alkoxy;
- 4) -C₁₋₄alkyl-phenyl, wherein the phenyl is either unsubstituted or substituted with one or two substituents selected from:

a) -C₁₋₄ alkyl,

b) -halo,

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- 5
- e) -OH,
 - d) -CF₃,
 - e) -NH₂,
 - f) -NH(C₁₋₄ alkyl),
 - g) -N(C₁₋₄ alkyl)₂,
 - h) -CO₂H,
 - i) -CO₂(C₁₋₄ alkyl), and
 - j) -C₁₋₄ alkoxy;

10 R1b is selected from the group consisting of:

- 1) R1a,
- 2) -C₃₋₇ cycloalkyl, and
- 3) -CH₂-R1a;

15 R2a and R2b are independently phenyl, either unsubstituted or substituted with one or two substituents selected from the group consisting of:

- 20
- 1) -C₁₋₄ alkoxy,
 - 2) -halo,
 - 3) -OH,
 - 4) -CF₃,
 - 5) -NH₂,
 - 6) -NH(C₁₋₄ alkyl),
 - 7) -N(C₁₋₄ alkyl)₂,
 - 8) -CO₂H,
 - 25 9) -CO₂(C₁₋₄ alkyl), and
 - 10) -C₁₋₆ alkyl, either unsubstituted or substituted with one or more substituents selected from the group consisting of:
- 30
- a) -halo,
 - b) -OH,
 - c) -CF₃,
 - d) -NH₂,
 - e) -NH(C₁₋₄ alkyl),
 - f) -N(C₁₋₄ alkyl)(C₁₋₄ alkyl),
 - g) -CO₂H,

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- h) $-\text{CO}_2(\text{C}_{1-4} \text{ alkyl})$,
- i) $\text{C}_{1-4}\text{alkoxy}$,
- j) $-\text{S}(\text{O})_x(\text{C}_{1-4} \text{ alkyl})$ wherein
x is 0, 1 or 2, and
- 5 k) $-\text{C}_{3-7} \text{ cycloalkyl}$;

and the phenyl groups of R^{2a} and R^{2b} may be joined together at the ortho carbon atoms through a carbon-carbon single bond or C₁-3 alkylene to form a tricyclic group with the X² to which they are attached;

10 R³ is $-\text{CONR}^7\text{R}^8$;

R⁴, R⁵ and R⁶ are H;

15 R⁷ is C₁-6 alkyl substituted with one or more substituents selected from the group consisting of:

- 1) $-\text{N}(\text{R}^{10})(\text{CH}_2\text{CONHR}^{11})$,
- 2) $-\text{N}(\text{CO}_2\text{R}^{10})(\text{CH}_2\text{CONHR}^{11})$, and

R⁸ is H.

20

5. The compound of Claim 2 wherein:

R^{1a} is selected from the group consisting of:

- 1) H,
- 25 2) C₁-8 alkyl,
- 3) phenyl, either unsubstituted or substituted with one or two substituents selected from the group consisting of:
 - a) $-\text{C}_{1-4} \text{ alkyl}$,
 - b) -halo,
 - 30 c) $-\text{OH}$,
 - d) $-\text{CF}_3$,
 - e) $-\text{NH}_2$,
 - f) $-\text{NH}(\text{C}_{1-4} \text{ alkyl})$,
 - g) $-\text{N}(\text{C}_{1-4} \text{ alkyl})(\text{C}_{1-4} \text{ alkyl})$,
 - h) $-\text{CO}_2\text{H}$,

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- i) -CO₂(C₁₋₄ alkyl), and
j) -C₁₋₄ alkoxy;
- 5 4) -C₁₋₄alkyl-phenyl, wherein the phenyl is either
 unsubstituted or substituted with one or two substituents
 selected from:
- a) -C₁₋₄ alkyl,
 b) -halo,
10 e) -OH,
 d) -CF₃,
 e) -NH₂,
 f) -NH(C₁₋₄ alkyl),
 g) -N(C₁₋₄ alkyl)₂,
 h) -CO₂H,
15 i) -CO₂(C₁₋₄ alkyl), and
 j) -C₁₋₄ alkoxy;

R_{1b} is selected from the group consisting of:

- 20 1) R_{1a},
 2) -C₃₋₇ cycloalkyl, and
 3) -CH₂-R_{1a};

R_{2a} and R_{2b} are independently phenyl, either unsubstituted or substituted
with one or two substituents selected from the group consisting of:

- 25 1) -C₁₋₄ alkoxy,
 2) -halo,
 3) -OH,
 4) -CF₃,
 5) -NH₂,
30 6) -NH(C₁₋₄ alkyl),
 7) -N(C₁₋₄ alkyl)₂,
 8) -CO₂H,
 9) -CO₂(C₁₋₄ alkyl), and

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- 10) -C₁₋₆ alkyl, either unsubstituted or substituted with one or more substituents selected from the group consisting of:
- a) -halo,
 - b) -OH,
 - c) -CF₃,
 - d) -NH₂,
 - e) -NH(C₁₋₄ alkyl),
 - f) -N(C₁₋₄ alkyl)(C₁₋₄ alkyl),
 - g) -CO₂H,
 - h) -CO₂(C₁₋₄ alkyl),
 - i) C₁₋₄alkoxy,
 - j) -S(O)_x(C₁₋₄ alkyl) wherein
x is 0, 1 or 2,
 - k) -C₃₋₇ cycloalkyl;
- and the phenyl groups of R^{2a} and R^{2b} may be joined together at the ortho carbon atoms through a carbon-carbon single bond or C₁₋₃ alkylene to form a tricyclic group with the X² to which they are attached;
- R³ is -CONR⁷R⁸;
- R⁴, R⁵ and R⁶ are H;
- R⁷ is C₁₋₆ alkyl substituted with -NR¹⁰R¹¹;
- R⁸ is H;
- R¹⁰ is -(C₁₋₆ alkyl)-phenyl, wherein the phenyl is substituted with -C₁₋₄ alkoxy,
- R¹¹ is H, C₁₋₆ alkyl, or is independently selected from the definitions of R¹⁰.

6. The compound of Claim 2 wherein:

R^{1a} is selected from the group consisting of:

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- 1) H,
2) C₁₋₈ alkyl,
3) phenyl, either unsubstituted or substituted with one or two
substituents selected from the group consisting of:
- 5 a) -C₁₋₄ alkyl,
b) -halo,
c) -OH,
d) -CF₃,
e) -NH₂,
10 f) -NH(C₁₋₄ alkyl),
g) -N(C₁₋₄ alkyl)(C₁₋₄ alkyl),
h) -CO₂H,
i) -CO₂(C₁₋₄ alkyl), and
15 j) -C₁₋₄ alkoxy;
- 4) -C₁₋₄alkyl-phenyl, wherein the phenyl is either
unsubstituted or substituted with one or two substituents
selected from:
- 20 a) -C₁₋₄ alkyl,
b) -halo,
c) -OH,
d) -CF₃,
e) -NH₂,
f) -NH(C₁₋₄ alkyl),
25 g) -N(C₁₋₄ alkyl)₂,
h) -CO₂H,
i) -CO₂(C₁₋₄ alkyl), and
j) -C₁₋₄ alkoxy;
- 30 R_{1b} is selected from the group consisting of:
- 1) R_{1a},
2) -C₃₋₇ cycloalkyl, and
3) -CH₂-R_{1a};

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R^{2a} and R^{2b} are independently phenyl, either unsubstituted or substituted with one or two substituents selected from the group consisting of:

- 1) -C₁₋₄ alkoxy,
- 2) -halo,
- 3) -OH,
- 4) -CF₃,
- 5) -NH₂,
- 6) -NH(C₁₋₄ alkyl),
- 7) -N(C₁₋₄ alkyl)₂,
- 8) -CO₂H,
- 9) -CO₂(C₁₋₄ alkyl), and
- 10) -C₁₋₆ alkyl, either unsubstituted or substituted with one or more substituents selected from the group consisting of:
 - a) -halo,
 - b) -OH,
 - c) -CF₃,
 - d) -NH₂,
 - e) -NH(C₁₋₄ alkyl),
 - f) -N(C₁₋₄ alkyl)(C₁₋₄ alkyl),
 - g) -CO₂H,
 - h) -CO₂(C₁₋₄ alkyl),
 - i) C₁₋₄alkoxy,
 - j) -S(O)_x(C₁₋₄ alkyl) wherein
x is 0, 1 or 2,
 - k) -C₃₋₇ cycloalkyl;

and the phenyl groups of R^{2a} and R^{2b} may be joined together at the ortho carbon atoms through a carbon-carbon single bond or C₁₋₃ alkylene to form a tricyclic group with the X² to which they are attached;

R³ is CONR⁷R⁸;

R⁴, R⁵ and R⁶ are H;

R⁷ is C₁₋₆ alkyl substituted with -NR¹⁰R¹¹;

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R⁸ is H;

R¹⁰ is C₁₋₆ alkyl;

5 R¹¹ is H or C₁₋₆ alkyl.

7. The compound of Claim 2 wherein:

R^{1a} is selected from the group consisting of:

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- 1) H,
 - 2) C₁₋₈ alkyl,
 - 3) phenyl, either unsubstituted or substituted with one or two substituents selected from the group consisting of:
 - 15 a) -C₁₋₄ alkyl,
 - b) -halo,
 - c) -OH,
 - d) -CF₃,
 - e) -NH₂,
 - f) -NH(C₁₋₄ alkyl),
 - 20 g) -N(C₁₋₄ alkyl)(C₁₋₄ alkyl),
 - h) -CO₂H,
 - i) -CO₂(C₁₋₄ alkyl), and
 - j) -C₁₋₄ alkoxy;
 - 25 4) -C₁₋₄alkyl-phenyl, wherein the phenyl is either unsubstituted or substituted with one or two substituents selected from:
 - 30 a) -C₁₋₄ alkyl,
 - b) -halo,
 - c) -OH,
 - d) -CF₃,
 - e) -NH₂,
 - f) -NH(C₁₋₄ alkyl),
 - g) -N(C₁₋₄ alkyl)₂,
 - h) -CO₂H,

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- i) -CO₂(C₁₋₄ alkyl), and
- j) -C₁₋₄ alkoxy;

5 R1b is selected from the group consisting of:

- 1) R1a,
- 2) -C₃₋₇ cycloalkyl, and
- 3) -CH₂-R1a;

10 R2a and R2b are independently phenyl, either unsubstituted or substituted with one or two substituents selected from the group consisting of:

- 1) -C₁₋₄ alkoxy,
- 2) -halo,
- 3) -OH,
- 4) -CF₃,
- 15 5) -NH₂,
- 6) -NH(C₁₋₄ alkyl),
- 7) -N(C₁₋₄ alkyl)₂,
- 8) -CO₂H,
- 9) -CO₂(C₁₋₄ alkyl), and
- 20 10) -C₁₋₆ alkyl, either unsubstituted or substituted with one or more substituents selected from the group consisting of:
 - a) -halo,
 - b) -OH,
 - c) -CF₃,
 - 25 d) -NH₂,
 - e) -NH(C₁₋₄ alkyl),
 - f) -N(C₁₋₄ alkyl)(C₁₋₄ alkyl),
 - g) -CO₂H,
 - h) -CO₂(C₁₋₄ alkyl),
 - 30 i) C₁₋₄alkoxy,
 - j) -S(O)_x(C₁₋₄ alkyl) wherein
x is 0, 1 or 2,
 - k) -C₃₋₇ cycloalkyl;

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and the phenyl groups of R^{2a} and R^{2b} may be joined together at the ortho carbon atoms through a carbon-carbon single bond or C₁₋₃ alkylene to form a tricyclic group with the X² to which they are attached;

5 R³ is -CO₂R⁹;

R⁴, R⁵ and R⁶ are H;

10 R⁹ is H.

8. A compound which is selected from the group consisting of:

- 15 1) trans 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(2-(N-(aminocarbonylmethyl)amino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine;
- 20 2) trans 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-(N-(aminocarbonylmethyl)amino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine;
- 25 3) trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-2-(RS)-(2-(N-(benzyloxycarbonyl)-N-(aminocarbonylmethyl)amino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine;
- 30 4) trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-2-(RS)-(2-N-(aminocarbonylmethyl)amino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine;
- 5) trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-(N-aminocarbonylmethyl)amino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine;

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- 6) trans 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methylamino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine;
- 5 7) cis 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methylamino)ethylaminocarbonyl)-4-(SR)-(N,N-dipentylaminocarbonyl)piperidine;
- 10 8) trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methylamino)ethylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine;
- 15 9) trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-2-(RS)-(2-(N-(2-methoxybenzyl)-N-methylamino)ethylaminocarbonyl)-4-(RS)-(N,N-dibenzylaminocarbonyl)piperidine;
- 20 10) trans 1-(N,N-diphenylaminocarbonyl)-2-(RS)-(3-(diethylamino)propylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine;
- 25 11) trans 1-(N,N-diphenylaminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine-2-(RS)-carboxylic acid;
- 12) trans 1-(N-(3-chlorophenyl)-N-(phenyl)aminocarbonyl)-4-(RS)-(N,N-dipentylaminocarbonyl)piperidine-2-(RS)-carboxylic acid;

or a pharmaceutically acceptable salt thereof.

- 30 9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of the compound of Claim 1.

10. A method for antagonizing the effect of substance P at its receptor site or for the blockade of neurokinin-1 receptors in a

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mammal which comprises the administration to the mammal of the compound of Claim 1 in an amount that is effective for antagonizing the effect of substance P at its receptor site in the mammal.

5 11. A method for antagonizing the effect of neurokinin A at its receptor site or for the blockade of neurokinin-2 receptors in a mammal which comprises the administration to the mammal of the compound of Claim 1 in an amount that is effective for antagonizing the effect of neurokinin A at its receptor site in the mammal.

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 12. A method of treating or preventing pain or nociception attributable to or associated with migraine in a mammal in need thereof which comprises the administration to the mammal of an effective amount of the compound of Claim 1.

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 13. A method of treating or preventing a condition selected from the group consisting of: diabetic neuropathy; peripheral neuropathy; AIDS related neuropathy; chemotherapy-induced neuropathy; and neuralgia, in a mammal in need thereof which comprises the administration to the mammal of an effective amount of the compound of Claim 1.

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 14. A method for the treatment or prevention of asthma in a mammal in need thereof which comprises the administration to the mammal of an effective amount of the compound of Claim 1, either alone or in combination with a neurokinin-2 receptor antagonist or with a β 2-adrenergic receptor agonist.

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 15. A method for the treatment of cystic fibrosis in a mammal in need thereof which comprises the administration to the mammal of an effective amount of the compound of Claim 1.

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16. A method for the treatment or prevention of emesis in a mammal in need thereof which comprises the administration to the mammal of an effective amount of the compound of Claim 1.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/01800**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : C07D 211/06; A61K 31/445

US CL : 546/226; 514/315

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/226; 514/315

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,804,661 (FERRINI ET AL) 14 FEBRUARY 1989, See entire document	1-16
A	US, A, 5,019,576 (BRAQUET ET AL) 28 MAY 1991, See entire document.	1-16
A	US, A, 5,064,838 (CARR ET AL) 12 NOVEMBER 1991, See entire document.	1-16
A, P	US, A, 5,292,726 (ASHTON ET AL) 08 MARCH 1994, See entire document.	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	* T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
* A* document defining the general state of the art which is not considered to be of particular relevance	* X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
* E* earlier document published on or after the international filing date	* Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
* L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	* A*	document member of the same patent family
* O* document referring to an oral disclosure, use, exhibition or other means		
* P* document published prior to the international filing date but later than the priority date claimed		

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